Facilitating Regulatory Review: What the FDA Wants to See

58th Meeting of the National Cancer Institute Director's Consumer Liaison Group (DCLG)

September 22, 2011

Overview

- Clinical Development Programs
- Clinical Trial Endpoints
- Combination Products

Clinical Development Programs – Critical Path Initiative

FDA's Critical Path Initiative

- Created based on recognition that there is failure of science of drug development to keep up with science of drug discovery
- Recognizes concurrent evaluation of safety, efficacy, and manufacture of new drugs

Clinical Development Programs – General Principles

Clinical development an iterative process

- Manufacturing process changes may alter pharmacokinetics → impact safety & efficacy
- Accumulating clinical & non-clinical information should affect development plan
- Begin early in development to identify novel assays and to design co-development program for assays that enhance safe and effective use

Clinical Development Programs – FDA view

Goal of all clinical development programs

- Obtain data sufficient in quality and quantity to establish the safety and effectiveness with a high level of confidence
- Obtain data adequate to describe safe and effective use in product labeling

Clinical Development Programs

- Non-clinical studies to evaluate for
  - effects of chronic/long-term dosing, effects on fertility and embryofetal development, potential carcinogenicity
- Evaluate appropriateness of dose through
  - exposure-response relationships
  - exposure-toxicity relationships
  - food effects on drugs (oral)
  - possible drug interactions

Clinical Development Programs

Targeted safety assessments

- Evaluate need for dose adjustments based on kidney or organ dysfunction
- Evaluate potential cardiac effects (QT)
- Evaluate for differences in exposure based on gender, age, ethnicity or genetic factors

Phase 1 trials

- 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 and pharmacodynamic data

Phase 2 Trials

- Purpose:
  - Initial determination of activity
  - Further study of appropriate dose range
- Generally conducted in patients with measurable disease
- Considerations:
  - Number of patients exposed
  - Efficient determination of activity
  - Careful monitoring & characterization of toxicity

Phase 3 Trials

- Purpose: Further characterization of safety & effectiveness compared to control group
- Standards of effectiveness
  - Equivalent or superior activity relative to active (efficacious) control
  - Superior to inactive control or no treatment (if none is available)

Phase 4 Trials

- Purpose: Further assess safety & efficacy or assess new indications
- 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)

Clinical Development Programs

Ultimate Goal = Marketing Approval

- Requires demonstration that product is safe and effective
- There must be “substantial evidence of effectiveness”
- Product “safety” is considered in context of condition being treated, available alternative therapy, & product efficacy
- FDA refers to this as net clinical benefit (benefits outweigh risks)

Clinical Development Programs

- An intermediate goal of development may be marketing under accelerated approval
- Accelerated approval an option for drugs that
  - treat serious or life-threatening diseases
  - demonstrate an improvement over available therapy or provide therapy where none exists
  - show an effect on a surrogate endpoint that is *reasonably likely* to predict clinical benefit ("based on epidemiologic, therapeutic, pathophysiologic, or other evidence").

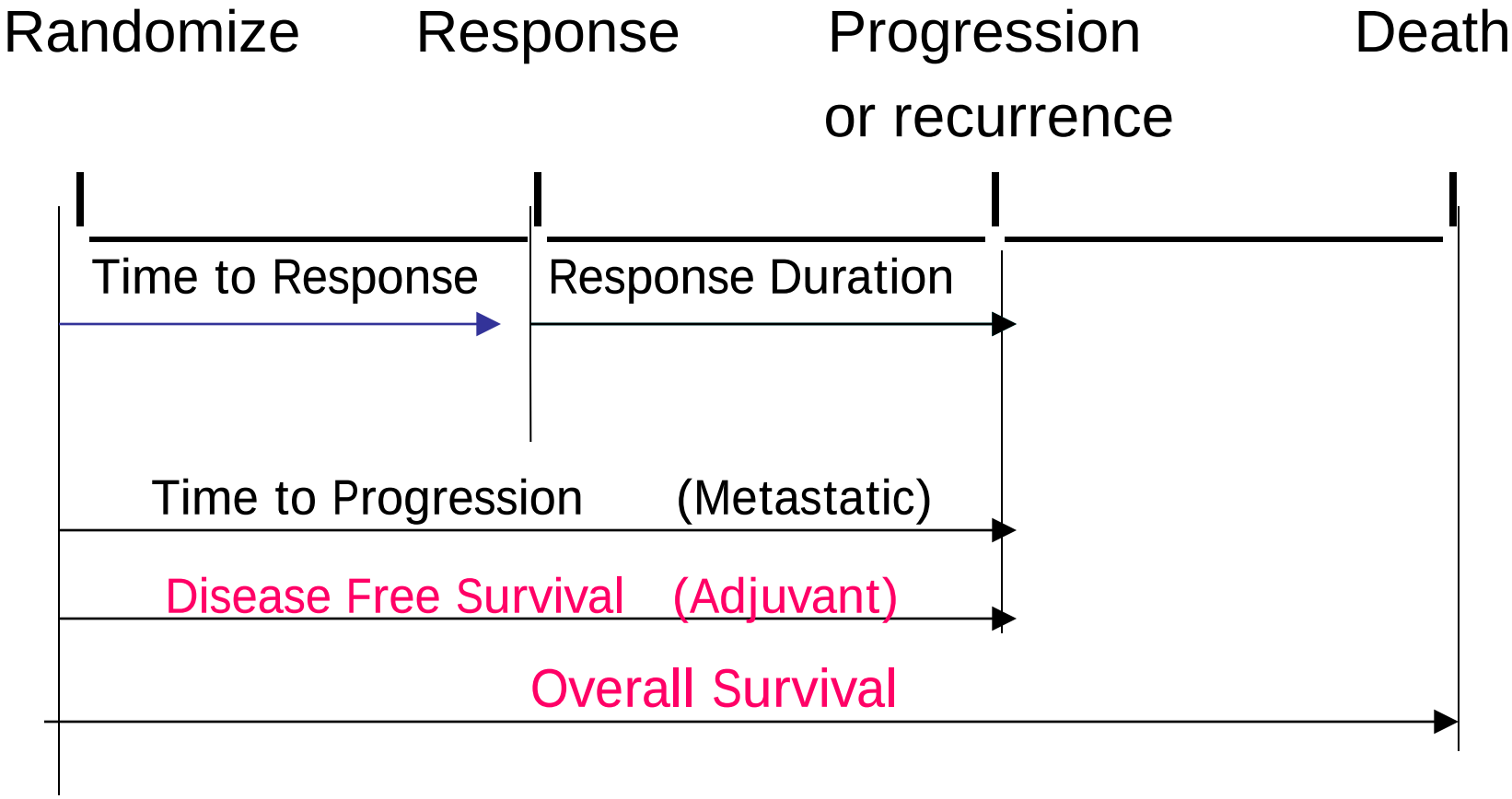
Clinical Trial Endpoints

Clinical Trial Efficacy Endpoints

Selection of endpoint depends on

- Drug's mechanism of action
- Prognosis of primary cancer & extent of disease
- Availability & efficacy of alternative treatments
- Intent to seek regular approval vs. accelerated approval

Clinical Trial Endpoints



Clinical Trial Endpoints

Direct evidence of clinical benefit

- Patients living longer
  - Measured as overall survival
- Patients living better
  - improvement in quality of life (QOL)
  - improved physical functioning
  - improved tumor-related symptoms

Trial Design Concerns

- Trials with survival endpoints
  - must assess in randomized trial
  - may require large sample size (small effect)
  - may take years to complete
- Trials with patient-reported outcomes
  - must assess in randomized trial
  - assessor must be masked to treatment
  - missing data undermines interpretation
  - lack of validated instruments

Clinical Trial Endpoints

"Established surrogates" for clinical benefit

- Longer disease-free survival (DFS) in some adjuvant settings (high likelihood of tumor-related symptoms with recurrence/relapse)
- Durable complete response in acute leukemias

- Durable objective response rate of clinically important magnitude and minimal drug toxicity (e.g., hormonal therapies)

Trial Design Concerns

Trials with tumor based endpoints

- must collect data for each tumor assessment;
- may need independent audit of selected patients or entire study

Trials with time-to-event endpoints

- Must be randomized and preferrably double-blind or have prospective plan for independent assessment

Clinical Trial Endpoints

Surrogate endpoints likely to predict benefit

- Durable objective tumor shrinkage
- Delay in time to disease progression
- Improvement in progression-free survival

Trial Design Concerns

Trials with tumor based endpoints

- must collect data for each tumor assessment;
- may need independent audit of selected patients or entire study

Trials with time-to-event endpoints

- Must be randomized
- double-blind or prospective plan for independent audit

Combination Products

Combination Products

21 CFR Part 3

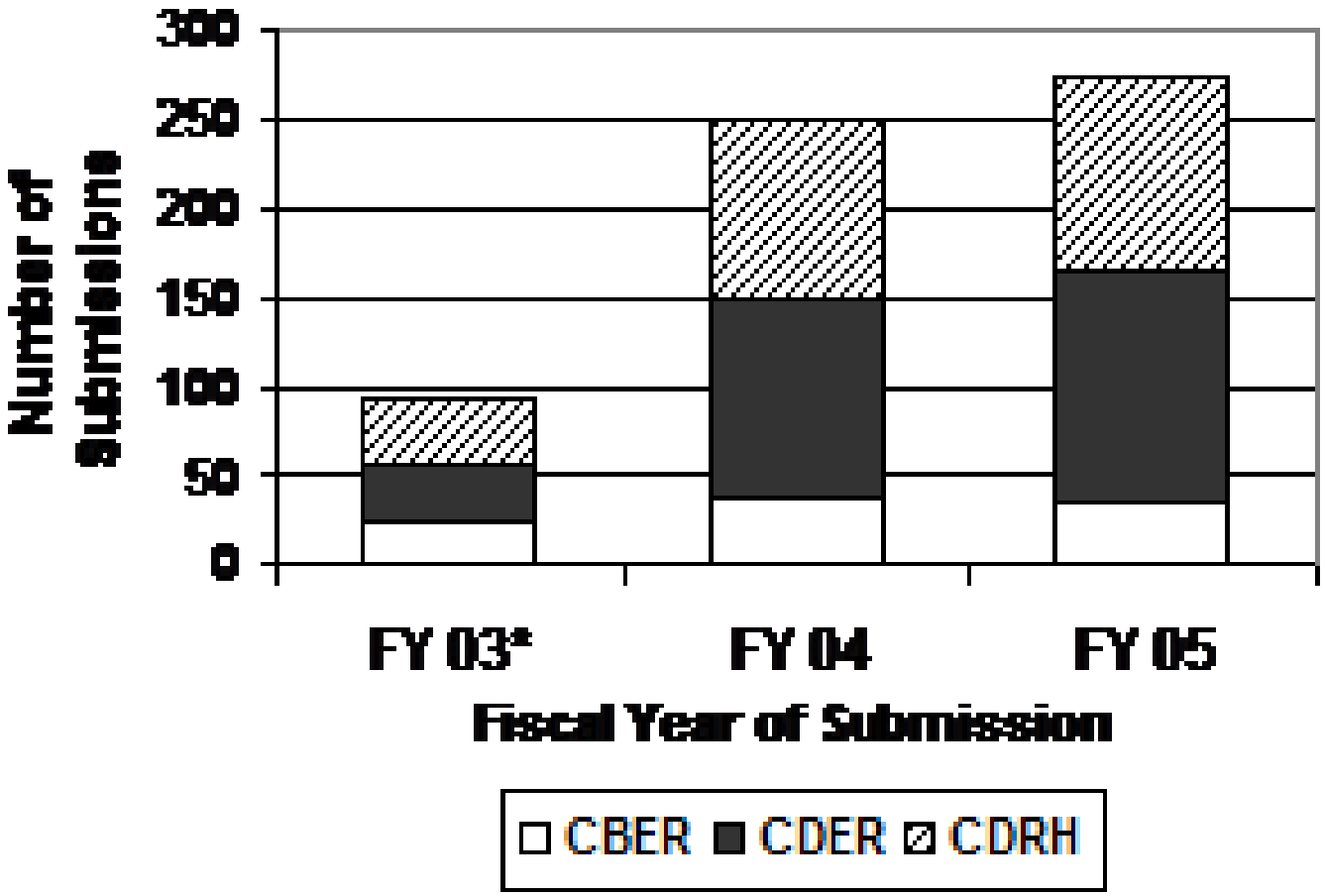
- Drug/biologic
- Drug/device
- Biologic/device
- Biologic/device/drug

Describes review Center designation based on primary mode of action

Combination Products

- Product comprised of two or more regulated components that are physically, chemically or otherwise combined or mixed as a single entity;
- Two or more separate products packaged together in a single package or a unit (e.g., drug and device products, device and biological products, or biological and drug products);
- A drug or device packaged separately but intended for use only with approved specified drug, device, or biological product and both are required for intended use; or
- Provided separately but intended for use together; both are required to achieve intended use, indication, or effect; <u>and</u> where mutually conforming labeling is needed.

Combination Product Applications



Combination Product Applications

- FDA received
  - 350 original applications for combination products in FY 2009
  - 311 original applications for combination products in FY 2010

Combination Therapies

General challenges:

- Clinical development programs designed to
  - Establish that each component is *required to achieve the intended use, indication, or effect*
  - Generate sufficient data to write adequate directions for use (patient population, dose/schedule, risks)
  - Conducted with product in which each component adequately characterized (GMP)

Combination Therapies

Guidance available to manufacturers on

- Jurisdiction for lead Center and role of Office of Combination Products
- Principles for regulatory review
- Expectations for expedited and general post-market safety reporting
- GMP requirements- Proposed rule on cGMP for combination products (9/2009) & Guidance for Industry (2004)

Combination Therapies

CMC Challenges

- Manufacturers will not provide access to or develop products for combination use
- CMC data may reside in Master Files or cross-referenced file not accessible to investigator; FDA cannot discuss/divulge CMC issues without authorization

Combination Therapies

Non-Clinical Challenges

- Establishing a safe starting dose/dose escalation for first-in-human studies
  - Standard assessments differ by product (drug/device/biologic) may be duplicative
  - Standard assessment for a specific type of product may not be fully informative for all components
  - Integrating information from each product
  - Identifying toxicities novel to combination

Combination Therapies

Recommended approach

- Per Guidance on Non-clinical Safety Evaluation of Drug or Biologic Combinations, non-clinical testing program should be designed with consideration of
  - Extent of prior human experience,
  - Information on individual components

  and address
  - Possibility of interactions (PK or PD)
  - Possibility of toxic interaction

Combination Therapies

Clinical Challenges

- Contribution of each agent in definitive trials may require multi-arm, parallel design trials; trial design analysis plan must be pre-specified
- Overall strength of evidence is considered; non-clinical data may provide compelling evidence of contribution to effect if it can be “bridged” to clinical outcomes

Combination Therapies

Identify supplemental information to support efficacy trials

- Characterize mechanism of action in non-clinical models/systems
- Characterize relationship between pharmacodynamic effects and clinical outcomes from non-clinical to clinical studies (bridging)
- Identification of “priors” from published literature/publicly available information

Combination Therapies

Supplemental information to combination efficacy studies

- Combinations where one or both agent is approved for a similar setting
- Obtain bridging information in “window of opportunity studies” or randomized Phase 2 study

Companion Diagnostics

Recently published draft Guidance for Industry for Companion Diagnostic Devices (docket open for public comment)

- Defines companion diagnostic *in vitro* device (IVD)
- Provides rationale for regulatory oversight
- States expectations for contemporaneous development & approvals of drug/IVD
- Discusses regulatory pre-approval pathways and enforcement policy

Companion Diagnostics

Definition

- in vitro companion diagnostic device that intended for use with corresponding therapeutic product that is necessary for safe and effective use of the therapeutic

Recently approved examples

- Zelboraf (vemurafenib) and cobas 4800 BRAF V600 Mutation Test
- crizotinib (XALKORI Capsules) and Vysis ALK Break-Apart FISH Probe Kit

Back up

Office of Oncology Reorganization

- Effective Sept. 12, 2011
- Office title change from Office of Oncology Drug Products (OODP) to Office of Hematology and Oncology Products (OHOP)
- Office headed by Richard Pazdur – no changes in immediate office
- 3 Review Divisions in OODP → 4 Divisions in OHOP
- Re-assignment of work & personnel

OHOP at-a-glance

- **130** total employees in OHOP
- **55** medical oncologists
- **39** pharmacists, nurses and non-clinical Ph.D.s;
- **19** medical oncologists, nurses, and pharmacists practicing

- **10** new drug indications approved in 2010
- **7** new molecular entities approved to date in 2011

Rationale for Re-Organization

- More disease-specific review approach required by complexity of treatments under development
- Aligns with organizational structure of leading cancer treatment centers, academic programs and NCI
- Greater clarity and more transparent interactions on requirements to bring cancer treatments to market
- Greater efficiencies that will better support getting cancer treatments to patients

New Divisions and Therapeutic Areas

- **Division of Oncology Products 1 (DOP 1):** Breast, Gynecologic & Supportive care, Genitourinary
- **Division of Oncology Products 2 (DOP 2)**: Lung/H&N; Gastrointestinal; Melanoma/Sarcoma; Neuro-oncology, Rare cancers, Pediatric Solid Tumors
- **Division of Hematology Products (DHP):** Benign Heme, Heme Malignancy, Heme Support
- **Division of Hematology Oncology Toxicology (DHOT)**

Divisional Structure

DOP1	DOP2	DHP	DHOT
Division Director Robert Justice	Division Director Patricia Keegan	Division Director Ann Farrell.	Division Director John Leighton
Breast; Gynecologic; Genitourinary & Supportive care (non-hematologic)	Gastrointestinal; Lung/Head & Neck; Neuro-oncology/Rare cancers/Pediatric Solid Tumor; Melanoma & Sarcoma	Benign hematology; Hematologic malignancies; Hematology support; Pediatric Hematology	Nonclinical Review Division for Hematology/ Oncology products

Combination Therapies – Example

131-I tositumomab (Bexxar)

- Extent of prior info for radioisotope
  - Effectiveness of radiotherapy in NHL well established
  - Pharmacokinetics (well characterized) and supported mechanism of action
- Contribution of mAb to radioisotope
  - Antitumor activity with mAb alone (Phase 2, imaging dose)
  - dose-dependent improvement in tumor localization with “cold” mAb

Efficacy Standard

- Demonstrate substantial evidence of effectiveness
  - "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effects it purports or is represented to have…"