



HORIZONS

Think. Challenge. Excel.

2008 RAPS HORIZONS CONFERENCE & EXHIBITION
26-28 March 2008 • San Francisco • The Fairmont

Decision Making in The Gray Zone: Addressing Unmet Medical Need in Fast Track Products

Steven Kradjian
Conventus Biomedical Solutions, Inc.




RAPS REGULATORY AFFAIRS
PROFESSIONALS SOCIETY
Making better healthcare products possible

Decision Making in The Gray Zone: Fast Track Products

Overview of Presentation

- Drug Approval Evidence Standards
- Key Features of Fast Track in Accelerating Drug Development
- Gray Zones
 - Standards of Evidence
 - Use of Surrogate Markers
 - Potential to Address Unmet Medical Need



2008 RAPS HORIZONS CONFERENCE & EXHIBITION
Making better healthcare products possible

Basis of Approval of a New Drug

- **Molecular and Preclinical Evaluation**
 - molecular structure and binding characteristics, in vitro biologic effects, animal models of safety and efficacy
- **Clinical Evaluation**
 - pharmacology, pharmacodynamics, exploratory clinical studies, confirmatory clinical trials

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Evidence Standards for Drug Approval

- **Preclinical studies**
 - Safe to proceed to first-in-man trials
- **Reprotoxicology, Carcinogenicity**
 - To support long term clinical use
- **Clinical studies**
 - To demonstrate safety and efficacy for an intended use

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



New Drug Approval Evidence

- Food Drug and Cosmetic Act
 - New drug application
 - Full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use.
 - A drug will be approved unless
 - Does not include adequate tests by all methods reasonably applicable to show whether a drug is safe
 - There is a lack of substantial evidence that the drug will have the effect that it purports

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Substantial Evidence

- Safety
 - Adequate tests by all reasonable methods
- Efficacy
 - Substantial evidence
 - Full reports of investigations
 - Adequate and well-controlled clinical trials

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



FDA Modernization Act and Fast Track

Evidence

- Possibility of single pivotal trial with heightened importance on pre-specified endpoints and analysis plan
- Abbreviated reports for some studies; full reports for safety data and efficacy from key studies
- Fast Track: Accelerated Approval, Priority Review

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Fast Track Products

- Food Drug and Cosmetic Act
 - Amended by FDA Modernization Act to include section 506: Fast Track products
 - Authorizes FDA to
 - Facilitate Development
 - Expedite Review
 - Incorporates Priority Review

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



FD&C Act Sec. 506 (a): Fast Track Products

- The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if
 - it is intended for the treatment of a serious or life-threatening condition and
 - it demonstrates the potential to address unmet medical needs for such a condition.

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Priority Review

- CDER
 - Products which, if approved, have the potential to provide, in the treatment, diagnosis, or prevention of a disease, one of the following: (1) Safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products
 - CDER MAPP 6020.3
- CBER
 - Products which provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease.
 - CBER SOPP 8405

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Accelerated Approval: Standard

- FDAMA permits approval
 - “upon determination that the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.”
 - FD&C Act, Section 505(c) or
 - PHS Act, Section 351

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Accelerated Approval: Main Features

- Main Features
 - Surrogate markers likely to predict clinical benefit, based on evidence from adequate and well controlled trials
 - Unmet medical need in a serious or life threatening condition
 - Adequate safety data
 - Confirmatory trials underway to demonstrate clinical benefit

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Accelerated Approval: Evidence

- Drugs: 21 CFR §314.510
- Biologics: 21 CFR §601.41
- FDA may grant marketing approval for a new drug on the basis of **adequate and well-controlled clinical trials** establishing that the drug product has an effect on a **surrogate endpoint** that is reasonably likely, *based on epidemiologic, therapeutic, pathophysiologic, or other evidence* to **predict clinical benefit** or on the basis of an effect on a **clinical endpoint other than survival or irreversible morbidity**.

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Gray Zone: Surrogate Marker / Surrogate Endpoint

- Surrogate Marker
 - A laboratory measurement, sign or symptom, that if changed by a therapy, would not in and of itself be clinically significant enough as a basis to evaluate therapeutic success.
- Surrogate Endpoint
 - A pre-defined change in a surrogate marker that is a primary or secondary outcome of a treatment trial.

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Surrogate Markers

Examples:

- Molecular markers
- Disease status measures
- Pharmacodynamic outcomes
- Drug mechanism based outcomes
- Prognostic assessments

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Gray Zones with Surrogate Markers

- Need to validate: need clinical trials to measure both clinical outcomes and surrogate markers.
- Specificity: need to show that surrogate marker reflects the clinical outcome.
- Power: if surrogate marker imprecisely predicts clinical outcome, need large trials or strong clinical effects

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Gray Zone: Addressing an Unmet Medical Need

In Serious or Life-Threatening Conditions:
Whether a condition is serious

“... is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease if left untreated would progress from a less severe condition to a more serious one.”

(57 FR 13234 April 15, 1992)

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Serious or Life Threatening Conditions

Examples:

- AIDS and HIV
- Alzheimer's Dementia
- Heart Failure
- Cancer
- Inflammatory Bowel Disease
- Diabetes Mellitus
- Rheumatoid Arthritis
- Depression
- Many others

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Gray Zone: Serious or Life Threatening Conditions

- Whether a drug is intended to treat serious conditions
 - Therapy directed at serious symptoms or serious manifestations of the condition
 - Diagnostic evaluated for the impact on a serious aspect of the condition
 - Preventive intended to prevent a serious aspect
 - Product which could ameliorate serious side effects of other treatments

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Potential to Address Unmet Medical Need

- A medical need not met by existing therapy
 - No existing or available therapy*
 - New therapy provides improved outcomes
 - New therapy for patients intolerant or unresponsive to existing therapy
 - New therapy is less toxic, similar benefit
 - New therapy improves compliance which is shown to improve effects on serious condition
 - New therapy is safe and effective in new subpopulation

* Available therapy: also existing treatment, existing therapy
Interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions, such as effectiveness that is well-documented in literature.

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



The Gray Zone: Addressing Unmet Medical Need

- Demonstrating the potential of a drug development program to meet an unmet medical need
 - Early development stages
 - Pharmacology data, animal models
 - Theoretical potential to meet unmet medical need
 - Later development stages
 - Clinical data
 - Efficacy comparison to approved treatments
 - Safety comparison to available treatments

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Gray Zone: Continuing to Address Unmet Medical Need

- A fast track drug development program may no longer meet the criteria if it no longer demonstrates potential to address unmet medical needs, for example:
 - if a new product were approved under a conventional approval that addressed the same needs, or
 - if emerging clinical data failed to show that the product in a fast track development program had the anticipated advantage over existing therapy.

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Decision-Making in the Gray Zone

- Where development plan is designated Fast Track, or seeks Accelerated Approval
 - Plan for and monitor evolving standards of care
 - Look for FDA requirements evolving with experience
- Use Special Protocol Assessments prudently
- Monitor developments at Advisory Committee meetings



HORIZONS

Think. Challenge. Excel.


2008 RAPS HORIZONS CONFERENCE & EXHIBITION
26-28 March 2008 • San Francisco • The Fairmont

To Report Or Not To Report: Is There A Question?

Alan G. Minsk
Partner and Chair,
Food and Drug Practice Team
Arnall Golden Gregory LLP
alan.minsk@agg.com




RAPS REGULATORY AFFAIRS
PROFESSIONALS SOCIETY
Making better healthcare products possible



Drug Reports

- With limited exception, all adverse drug experiences (ADEs) must be reported to FDA
- An ADE is any adverse event associated with the use of a drug in humans, whether or not considered drug-related



2008 RAPS HORIZONS CONFERENCE & EXHIBITION
Making better healthcare products possible

Drug Reports

(cont'd)

- An adverse event includes:
 - occurring with the drug's use in professional practice
 - from drug overdose (whether accidental or intentional)
 - drug abuse
 - drug withdrawal
 - any failure of expected pharmacological action

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Types Of Reports

- Depending on the type of ADE, the drug application holder must notify FDA in a 15-day alert report or a periodic report
 - we will not discuss here the criteria

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Screening

- FDA must conduct a bi-weekly screening of its Adverse Events Reporting System and post a quarterly report on FDA's website of any new safety information or potential safety signals based on the reviews

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Postmarket Drug Safety Information For Patients And Providers

- FDA must develop a website that will provide drug safety information
- The website must contain, among other things, patient and professional labeling, recent safety information, publicly available information about Risk Minimization Action Plans and Risk Evaluation and Mitigation Strategy, drug safety guidance documents and regulations, and drug-specific summary analyses of adverse drug reaction reports

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



Medical Device Reports

- Unless an exemption or variance applies, device manufacturers must report serious device-related adverse events
 - deaths and serious injuries that a device has or may have caused or contributed to, as well as certain device malfunctions
- Must also submit specified follow-up and baseline reports

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



So How Do You Comply With FDA's Requirements Without Increasing Liability Risk Exposure?

- The reporting of an ADE or an MDR does not constitute a conclusion or admission
- Failure to comply with the reporting requirements, however, may constitute negligence in a product liability context

2008 RAPS HORIZONS CONFERENCE & EXHIBITION



So How Do You Comply With FDA's Requirements Without Increasing Liability Risk Exposure?

(cont'd)

- Remember that anyone may report an ADE or MDR, so a company needs to consider that someone, even if not it, may notify FDA of a problem
 - at least investigate