Expedited Programs for Serious Conditions: Drugs and Biologics

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Expedited Programs

- Four FDA programs intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition:
  - **Fast track designation**
  - **Breakthrough designation**
  - **Accelerated approval**
  - **Priority review designation**

Serious Disease or Condition

Whether A Condition Is Serious

- A disease or condition associated with morbidity that has substantial impact on day-to-day functioning
  - the morbidity need not be irreversible if it is persistent or recurrent.
  - Seriousness of the disease is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Whether the Drug Is Intended to Treat a Serious Condition

- To satisfy this criterion, a drug must be intended to have an effect on a serious aspect of a condition, such as a direct effect on a serious manifestation or symptom of a condition, or other intended effects

Qualifying Criteria for FDA's Expedited Programs for Serious Conditions

Fast Track

- A drug that is intended to treat a serious condition **AND** nonclinical or clinical data demonstrate the potential to address unmet medical need **OR**
- A drug that has been designated as a qualified infectious disease product

Examples

- Nemonoxacin (Taigexyn®) Qualified Infectious Disease Product (QIDP) and Fast Track designations for community-acquired bacterial pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSS)

http://www.drugs.com/clinical_trials/nemonoxaci n-gets-fda-fast-track-designation-16405.html

- Tovaxin® for the treatment of patients with Secondary Progressive Multiple sclerosis (SPMS)

http://www.news-medical.net/news/20111108/FDA-grants-Fast-Track-designation-to Opexas-Tovaxin-for-treatment-

Breakthrough Therapy

- A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies

Example

- "Portola Pharmaceuticals Receives Breakthrough Therapy Designation From FDA for Andexanet Alfa (PRT4445*), Investigational Factor Xa Inhibitor Antidote."

  (http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsArticle&ID=1879666&highlight=)

Accelerated Approval

A drug that treats a serious condition **AND** generally provides meaningful advantage over available therapies **AND** demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (an intermediate clinical endpoint)

Example

- Accelerated Approval of Oncology Products: A Decade of Experience

Oxford Journals Medicine JNCI J Natl Cancer Inst Volume 96, Issue 20, Pp. 1500-1509

Priority Review

- An application (original or efficacy supplement) for a drug that treats a serious condition **AND** if approved, would provide a significant improvement in safety or effectiveness OR
- Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505Ac OR
- An application for a drug that has been designated as a qualified infectious disease product OR
- Any application or supplement for a drug submitted with a priority review vouchers

Kcentra Approval

- Product: a sterile, heat-treated, non-activated, nano-filtered, and lyophilized four-factor Prothrombin Complex Concentrate (PCC)
- Indication: for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with
  - acute major bleeding or
  - need for an urgent surgery/invasive procedure

Study design and Endpoints

- Randomized, open-label plasma-controlled non-inferiority trial in subjects receiving VKA therapy with major acute bleeding or undergoing invasive procedure /urgent surgery and whose baseline International Normalized Ratio (INR) was > 2.0
- The primary efficacy endpoint was the hemostatic efficacy as assessed from either the start of end of the test product infusion (depending on the type of bleeding) through 24 hours
  - Assessed by the blinded Independent Endpoint Adjudication Board (EAB) implemented by the data and safety monitoring board (DSMB).
  - Hemostatic efficacy ratings were made in accord with the EAB Charter as excellent, good, or poor/none, based on pre-specified definitions

Endpoints (contd.)

- Specific criteria were established *a priori*, depending on whether bleeding was
  - visible or fell into one of the following 3 non-visible bleeding categories:
    - Muscular/skeletal bleeding
    - Intra-cerebral hemorrhage (ICH)
  - Non-visible bleeding not listed above (such as GI or retro-peritonal bleeding)
- Co-primary endpoint:
  - proportion of subjects who had a decrease of the INR (< 1.3) at 30 minutes after end of infusion

Rationale for the Study Design and Choice of Primary Endpoints

- No RCTs using plasma for this indication were available to inform the selection of the non-inferiority margin, which was set at 10% (absolute, not relative percentage) for the primary hemostatic efficacy endpoint (excellent or good = effective vs. poor or none = not effective).

Rationale (contd.)

- FDA required a trial design that included hemostatic efficacy rather than solely relying on INR correction as the primary endpoint because:
  - animal data had indicated that abnormal hemostasis could persist despite INR correction (Dickneite G., *Thrombosis Research* 119:643-51 (2007) and
  - human data to show that INR could be relied upon to predict hemostasis in the context of VKA anticoagulation reversal using PCC were lacking (Kessler CM, *J. Thrombosis and Haemostasis* 4:963-966, 2006).

Rationale (contd.)

- The clinical trial was designed so that, if non-inferiority were demonstrated for the primary hemostatic endpoint and the co-primary INR correction endpoint, superiority testing would also be performed.

  – Non-inferiority was demonstrated in the primary hemostatic endpoint and the co-primary INR correction endpoint, however, superiority was not demonstrated for the primary hemostatic endpoint despite more rapid INR correction having been demonstrated with Kcentra than with plasma.

Thank You!!!