Alternative Regulatory Pathways: Opportunities and Challenges

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Outline of Presentation

- In this presentation I will discuss alternative regulatory pathways that have been implemented by the US Food and Drug Administration.

- I will describe how these pathways have been used to facilitate the evaluation, licensure and use of new vaccines.

- I will discuss the challenges of using these regulatory mechanisms to evaluate vaccines for emerging infectious diseases and use of these vaccines outside the US.

Introduction

- Alternative regulatory pathways have been created by the US Food and Drug Administration, and European Medicines Agency to expedite licensure or marketing authorization of certain human medical products.
- Some other countries may have similar, but not necessarily equivalent programs.
- One of the challenges of using these alternative regulatory pathways is the lack of standardization of requirements across regulatory authorities needed to support the universal acceptance of products approved under these pathways.
- The World Health Organization, although not a regulatory authority, develops standards for setting national regulatory recommendations, and many countries around the world look to the WHO for the purposes of using WHO standards as a basis for setting national regulatory requirements.

Expedited Pathways to Vaccine Development and Licensure: Fast Track Designation

- Authority: Section 506(a), FD&C Act
- Submit with IND; no later than pre-BLA
- Qualifying criteria
  - Treat a serious condition
  - AND data demonstrating potential to meet an unmet medical need
  - Evidence not required to be clinical data (theoretical or mechanistic rationales, or evidence of nonclinical data sufficient)
- Features
  - Opportunities for frequent interactions with the FDA review team
    - Pre-IND, end of Phase 1, end of Phase 2 meetings; “other meetings as appropriate”
    - Could be eligible for priority review if supported by clinical data at the time of the BLA submission
  - Eligible for “rolling review” of BLA submission (review of portions of the submission prior to submission of complete BLA)

Expedited Pathways: Breakthrough Therapy

- Authority: Section 506(a), FD&C Act
- Submit with IND; no later than end-of-Phase 2 meeting
- Qualifying criteria
  - Treat a serious or life-threatening disease or condition
  - May demonstrate substantial improvement over existing therapies
    - On one or more CLINICALLY SIGNIFICANT endpoints
    - Based on preliminary CLINCAL evidence
  - Note key difference with fast track designation: CLINICAL evidence required for breakthrough designation
- Features
  - Encompasses all fast track designation features
  - FDA to provide intensive guidance on efficient vaccine development during IND development phases
    - "Timely advice and interactive communications"
    - Agency may suggest alternative clinical trial designs (e.g., adaptive designs, enrichment strategies, use of historical controls) to expedite product assessment
  - Commitment to intensively involve senior FDA managers

Expedited Pathways: Accelerated Approval

- This process is relevant to the expedition of licensing (approval or marketing authorization) new products
  - Authority: 21 CFR 601 Subpart E: **Accelerated Approval** of Biological Products for Serious or Life-Threatening Illnesses
  - Provide "meaningful therapeutic benefit over existing therapies" (21 CFR 601.40)
  - Licensure based on demonstration of "effect on a surrogate endpoint reasonably likely…to predict clinical benefit…or on the basis of an effect on a clinical endpoint other than survival or irreversible mortality" (21 CFR 601.41)
- For vaccines: surrogate marker often = antibody titers known to prevent morbidity or mortality in natural infection or in past vaccine trials
- A conditional licensure
  - Requires a "Phase 4" post-marketing study with clinical endpoints to obtain FULL licensure
  - Phase 4 study should be underway prior to granting conditional marketing approval

Expedited Pathways: Priority Review

- Authority: Prescription Drug User Fee Act (PDUFA) of 1992
- Submit with original BLA (or efficacy supplement)
- Qualifying criteria (selected)
  - Treats a serious medical condition AND
  - Would provide a significant improvement in safety or effectiveness
  - OR – any application with a priority review voucher
- Features
  - Six month clock for BLA review (shortened from standard 10 month review)
  - Vaccines receiving fast track or breakthrough therapy designations frequently qualify for priority review

The "Animal Rule"

- Authority: 21 CFR 601 Subpart H: Approval of Biological Products when Human Efficacy Studies are Not Ethical or Feasible
  - For "serious or life-threatening conditions" (lethal or permanently disabling toxic biological, chemical, radiological or nuclear substances)
  - Field trials infeasible; human challenge unethical
  - A pathway of last resort: inapplicable if any other licensure pathway can be applied (21 CFR 601.90)
- Efficacy data acceptable from "well-controlled ANIMAL EFFICACY studies" (21 CFR 601.91)
- Vaccine "reasonably likely" to produce clinical benefit

The “Animal Rule”

- Four Key Criteria
  - Animal models reflect human pathogenesis;
  - Demonstrate effect of intervention in more than one animal species;
  - Animal study endpoint should be clearly related to desired benefit in humans;
  - Studies should allow selection of effective dose in humans
- Full safety studies in humans required prior to licensure
- Phase 4 studies required if/when “event” occurs
- To date, no vaccine licensed under the Animal Rule
  - *Post-exposure prophylaxis (with concomitant antibiotic use) indication was approved using the Animal Rule*

Regulatory Harmonization and Convergence

- A process whereby regulatory requirements across regions/countries become more aligned based on acceptance of scientific principles, common or similar practices and procedures.
  - Does not necessarily mean harmonization of laws and regulations
- Development of technical guidelines that are uniform across participating regulatory authorities
- To streamline the regulatory processes in various countries, efforts have been undertaken to harmonize international standards and norms.
- When it is not possible to harmonize regulations due to varying legislative frameworks, efforts have continued toward reaching regulatory convergence.
- For large markets in certain developed countries, the International Conference on Harmonisation was organized in 1990 (renamed the International Council for Harmonisation.
- To aid regulators in all markets, including the low- and middle-income countries (LMIC), the WHO has taken the lead.

Organizations Involved In Regulatory Convergence Or Harmonization Efforts

- The Developing Country Vaccine Manufacturer's Network (DCVMN)
  - promotes harmonization and solutions to challenges that manufacturers in developing countries face.
- The Asia-Pacific Economic Cooperation (APEC) Harmonization Center (AHC) "established under the authority of the APEC Life Sciences Innovation Forum (LSIF).
  - supports access to the best practices and guidelines for regulatory harmonization in the sector of Life Science.
  - promotes collaborative actions and wide information exchanging activities among the participants

WHO Joint Evaluations by NRAs

- Multiple ongoing initiatives led by WHO in order to support strengthening of regulatory systems
  - Developing Countries' Vaccine Regulators Network (DCVRN)
  - African Vaccine Regulatory Forum (AVAREF)
- Joint review of a phase 3 trial of the RTS,S malaria vaccine was coordinated under the AVAREF framework.
- WHO conducted regulatory training exercises for NRAs that supported the prompt registration of MenAfriVac.
- WHO also supports the strengthening of regulatory systems by using a standardized benchmarking tool and providing targeted technical assistance to help bring each NRA to a functional, stable level of operation.

EMA-FDA Parallel Scientific Advice

- Provides a mechanism for parallel scientific advise to sponsors
- EMA assessors and FDA reviewers concurrently exchange views on scientific issues during development phase of new medicinal products
- PSA procedures conducted under auspices of confidentiality arrangement between European Commission, the EMA and US FDA
- After PSA procedure, each agency retains its individual regulatory decision-making authority regarding drug development issues and marketing applications
  - The advise of each agency may still differ after the joint discussion
- Each agency provides its independent advise on questions posed during the PSA process according to usual procedures and timelines.

Summary

- Alternative regulatory pathways, have been developed by the US FDA and other national regulatory authorities to facilitate the access of promising human medical products.
- Special regulatory pathways are also intended to facilitate the development of products that may not otherwise be developed.
- Despite the availability of these pathways, the development of products for use against emerging infectious diseases has been slow due to many reasons
  - Inadequate science
  - No commercial market
  - No clear regulatory pathway to licensure

Session P4:
Regulatory Capacity, Challenges and Convergence

- Challenges
  - Technological advances that accelerate vaccines along the regulatory pathway and into the clinic
  - Utility of non-clinical efficacy data when clinical safety data are limited or efficacy data is available
  - Approaches to reduced dose schedules
  - Identifying correlates of protection for the public good
- Capacity
  - How to ensure efficient product development and regulatory decision making in a complex environment with relatively low capacity
  - Strengthening regulatory science in LMIC
- Convergence
  - Who drives regulatory standards
  - Regulatory harmonization and preparedness for emerging infectious diseases

Thank You!

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Backups

Additional points

- What would be helpful:
  - Standardized protocols to support Phase 1&2 studies to enable quick starts in clinic when time is of the essence.
  - Standardized approaches to post market surveillance (across world) to ensure follow-up.
  - Greater support for efforts to adopt Emergency Use Authorization globally as available in the US
  - Support WHO in building post market surveillance capacity for both safety and effectiveness
  - Establish background rates for serious adverse events to help in evaluating causation when adverse events are detected post vaccination.