How to Get a New Drug Approved by the FDA

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- Laws and regulations
- FDA role in drug development and approval
- Examples of clinical trial designs, endpoints, and results used to support the approval of drugs to treat prostate cancer

Laws and Regulations

- Federal Food, Drug, and Cosmetic Act of 1938 required drugs be shown to be safe prior to marketing
- Public Health Service Act of 1944 provided for the regulation of biological products
- Kefauver-Harris Drug Amendments of 1962 required proof of efficacy prior to marketing
- Code of Federal Regulations, Title 21
  - IND regulations: Part 312
  - NDA regulations: Part 314
  - Biologic licensing regulations: Part 601

FDA & Drug Development

- Pre-IND Meetings
- Investigational New Drug Application (IND)
- End-of-Phase 2 Meetings
- Special Protocol Assessments
- Pre-NDA Meetings
- New Drug Application (NDA)
- Post-marketing activities

Pre-IND Meetings

- Purpose is to ensure adequacy of an IND submission
- Discuss questions posed by the drug sponsor regarding
  - Chemistry, manufacturing and controls
  - Non-clinical pharmacology and toxicology studies
  - Previous clinical data, if any
  - Proposed clinical study or studies

Investigational New Drug Application (IND)

- Required to conduct clinical studies with an investigational drug involving interstate commerce
- IND submission contains information on CMC, non-clinical pharmacology and toxicology studies, previous clinical data (if any), and clinical protocols
- FDA has 30 days to review initial submission
- Subsequent clinical studies may begin as soon as the protocols are submitted
- FDA reviews all protocols, protocol amendments, adverse event reports, study reports and annual reports

End-of-Phase 2 Meetings

- Requested by IND sponsor to discuss questions concerning CMC, non-clinical and clinical pharmacology, toxicology, and proposed phase 3 studies
- Purpose is to ensure that the drug development plan is adequate to support a new drug application
- Particular emphasis is placed on reaching agreement on the design of phase 3 studies

Special Protocol Assessment

- Requested by IND sponsor, generally after an end-of-phase 2 meeting
- Goal is to reach agreement on protocol design
- FDA has 45 days to review proposed protocol, statistical analysis plan, case report forms, and questions posed by the sponsor. FDA may take longer if an outside consultant is required.
- If agreement is reached, the SPA is a commitment by FDA that depending on the results the study will support filing of a new drug application
- Significant protocol amendments must be agreed to in writing by FDA and IND sponsor

Pre-NDA Meetings

- Requested by IND sponsor to discuss
  - Adequacy of CMC, non-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics information
  - Adequacy of clinical study results to support approval
  - Format and content of the application

New Drug Application

- Contains proposed labeling and detailed technical sections:
  - CMC and microbiology (if applicable)
  - Non-clinical pharmacology and toxicology
  - Human pharmacokinetics and bioavailability
  - Clinical data, including study protocols and all amendments, study reports, case report forms and CRF tabulations
  - Statistical evaluation of the clinical data

New Drug Application

- Reviewed by a multidisciplinary team of physicians, statisticians, chemists, pharmacologist/toxicologists, clinical pharmacologists, and microbiologists
- FDA has 6 months to take an action on a priority application and 10 months for a standard application
- Most applications are either discussed with an FDA consultant or at a meeting of the Oncologic Drugs Advisory Committee (ODAC)

Post-Marketing Activities

- Supplemental New Drug Applications for new indications
- Post-marketing surveillance of adverse events (www.fda.gov/medwatch)
- Labeling changes for safety and Dear Health Care Practitioner letters

New Indications

- Require a supplemental NDA containing
  - Proposed labeling changes
  - Clinical data, including study protocols and all amendments, study reports, CRF's and CRF tabulations
  - Statistical evaluation of the clinical data
- Primarily reviewed by physicians and statisticians
- Same timelines for priority and standard reviews as an NDA
- May also involve an FDA consultant or ODAC

Study Designs for Advanced Prostate Cancer

- Statutory requirement for adequate and well-controlled investigations…
- Single-arm trials demonstrating castrate levels of testosterone have been used to support approval of GnRH agonists for the palliative treatment of hormone-sensitive advanced prostate cancer
- Randomized-controlled trials demonstrating improvement in pain or survival have been used to support approval of drugs for the treatment of advanced hormone-refractory prostate cancer

Drug Approval Based on Testosterone Levels

- One example of a leuprolide acetate formulation:
  - Open-label trial in 120 patients with advanced prostate cancer receiving Eligard™ (leuprolide acetate) 7.5 mg SC monthly x 6
  - Mean serum testosterone concentration was 361 ng/dL at baseline 575 ng/dL at day 3, below baseline by day 10, 22 ng/dL on day 28, and 6 ng/dL at month 6.
  - Testosterone was suppressed below ≤50 ng/dL in 94% of patients by day 28 and in all patients by day 42. No breakthrough was observed and all patients on study at month 6 had testosterone concentrations ≤50 ng/dL
  - AE's included hot flashes/sweats (57%), malaise/fatigue (18%), testicular atrophy (5%), dizziness (3%), gastroenteritis/colitis (3%), and local burning/stinging (35%), pain (4%), erythema (3%), and bruising (3%)

Drug Approval Based on Improvement in Pain

- Mitoxantrone was originally approved for the treatment of acute non-lymphocytic leukemia
- Approved 11/13/96 for use in combination with corticosteroids for the treatment of pain related to advanced hormone-refractory prostate cancer
- Approval was primarily based on results of the CCI-NOV22 trial.

CCI-NOV22 Trial Design

- Trial compared mitoxantrone plus prednisone (MP) to prednisone (P) in a randomized open-label trial
  - Mitoxantrone 12 mg/m^2 IV q 21 d plus prednisone 5 mg PO twice daily vs.
  - Prednisone 5 mg PO twice daily

CCI-NOV22 Trial Efficacy

- 161 symptomatic patients with HRPC were randomized
- The primary endpoint of palliative response was defined as a 2-point improvement on the 6-point Present Pain Intensity scale, accompanied by a stable analgesic score and lasting at least 6 weeks
- Palliative response rate was 29% on MP and 12% on P.
- Median duration of palliative response was 229 days on MP and 53 days on P (p=0.0001)
- Median survival was 11.3 months on MP vs. 10.8 months on P (P=0.23)

CCI-NOV22 Trial Safety

- Common (>10%) MP-related toxicities were neutropenia, fatigue, alopecia, anorexia, constipation, dyspnea, nail bed changes, edema, infection and mucositis
- 7/128 (5.5%) patients receiving MP had cardiac events, defined as decrease in LVEF < normal, CHF (n=3), or myocardial ischemia

Drug Approval Based on Survival

- Docetaxel was previously approved for the treatment of breast and NSCLC
- Approved 5/19/04 for use in combination with prednisone for the treatment of metastatic androgen-independent prostate cancer
- First and only approval of a drug to prolong survival in metastatic HRPC

TAX327 Design

- Compared MP to two schedules of DP in a randomized, open-label trial
  - Mitoxantrone 12 mg/m^2 IV q 21 d plus prednisone 5 mg PO twice daily
  - Docetaxel 75 mg/m^2 IV q 21 d plus prednisone 5 mg PO twice daily
  - Docetaxel 30 mg/m^2 IV weekly x 5 q 6 weeks plus prednisone 5 mg PO twice daily

TAX327 Efficacy

- 1006 patients with HRPC and no prior chemotherapy were randomized
- Survival was the primary efficacy endpoint
- DP q 3 weeks vs. MP: median survival 18.9 vs. 16.5 months (HR 0.76, p = 0.0094)
- DP weekly vs. MP: not significant
- Secondary endpoints of pain response rate & duration, PSA response rate & duration, time to pain progression, time to PSA progression, & TTP were considered exploratory

TAX327 Safety

Grade 3/4 (>2%)	DP	MP
Neutropenia:	32%	22%
Infection:	6%	4%
Anemia:	5%	2%
Fatigue:	5%	5%
Nausea	3%	2%
Diarrhea	2%	1%
Dyspnea	3%	1%

Conclusions

- Drugs for hormone-sensitive prostate cancer have been approved on the basis of castrate levels of testosterone
- Drugs for hormone-refractory prostate cancer have been approved on the basis of improvements in pain or survival
- Optimum drug development requires frequent interactions between the FDA and drug sponsors and investigators
- For more information (www.fda.gov)