What Every Advanced Practitioner Should Know About the FDA

Virginia Kwitkowski, MS, RN, ACNP-BC
Lead Clinical Analyst, Clinical Team Leader
Division of Hematology Products
FDA

Conflicts

• No financial conflicts

• I will not discuss off-label use of drugs

Topics

• FDA 101

• History of Advanced Practitioners at the FDA

• Expanded Access Programs at the FDA
FDA 101

- FDA mission: Protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.

- FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.

What are APs Doing at FDA?

- Clinical Reviewer
- Clinical Team Leader
- Deputy Director for Safety
- Associate Director for Labeling
- Regulatory Project Manager
- Nurse Scientist
- Safety Evaluator

Phases of Clinical Trials

<table>
<thead>
<tr>
<th>Phase of Trial</th>
<th>Purpose of Trial</th>
<th>Typical Size</th>
<th>Level of Evidence Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Early Pharmacokinetic/Pharmacodynamic Data</td>
<td>10-12</td>
<td>Should a new drug be tested?</td>
</tr>
<tr>
<td>1</td>
<td>Find a safe dose Pharmacokinetic data Pharmacodynamic Safety</td>
<td>15-30</td>
<td>What is the maximum tolerated dose or RP2D?</td>
</tr>
<tr>
<td>2</td>
<td>Assess Drug Activity Safety</td>
<td>&lt;100</td>
<td>Is the drug active enough to plan a Phase 3 trial OR Accelerated approval.</td>
</tr>
<tr>
<td>3</td>
<td>Compare new treatment to standard treatment</td>
<td>In oncology; from 100-1000s</td>
<td>Regular approval.</td>
</tr>
<tr>
<td>4</td>
<td>Evaluate post-marketing safety or efficacy; possibly a new indication</td>
<td>100-1000s</td>
<td>New indication, serve as a PMR.</td>
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</tbody>
</table>
Drug Development Timeline

Efficacy Endpoints and Approval Pathways

Endpoints of Direct Clinical Benefit:
- Higher Certainty
  - Response Rate in Solid Tumors
  - Overall Survival
  - DFS – Adjuvant Breast
- Lower Certainty
  - Clinical Chemistry
  - Pharmacology/Toxicology
  - Clinical Pharmacology

All Regulatory Approvals require Substantial Evidence from adequate and well-controlled clinical trials.

Regular approval:
- Endpoint: Based on prolongation of life, a better life or an established surrogate for either of the above

Accelerated approval for Severe or Life Threatening Diseases
- Provide meaningful therapeutic benefit to current therapies
- Endpoint: "Surrogate endpoint... reasonably likely... to predict clinical benefit"

Certainty of Clinical Benefit
- IND Received by FDA
- Divisional Assignment Made
- Clinical
- Clinical Pharmacology
- Toxicology
- Chemistry
- IND # Assigned

Clinical Deficiencies Identified?
- YES
- NO

Sponsor Response to FDA
- Deficiency Communicated to Sponsor
- IND May Proceed
How APs Accomplish the Mission

• Review INDs from initial safety review to the New Drug Application that may lead to a safe and effective new drug/biologic
• Guide the pharmaceutical industry in trial design, endpoint selection, trial implementation, and overall drug development strategies.
• Communicate important new approvals and safety information
• Monitor post-marketing safety, ensure accurate product labeling (Prescribing Information)

Advisory Committee Meetings

• Convened by FDA review divisions to discuss new applications, safety issues, etc.
• Provide independent advice to FDA
• Membership includes a chairperson, standing members, invited clinical experts (in the area of interest), statisticians, consumer representatives, industry reps (all carefully screened for conflict of interest)
• Hear presentations, discuss topics, and vote

How to Access Investigational Drugs
Expanded Access Programs
(Compassionate Use) 21CFR312(I)

- Use of investigational drug/biologic to treat a patient
- With a serious disease or condition
- Who does NOT have comparable or satisfactory alternative therapies (including a clinical trial for the product)
- Where the potential benefit justifies potential risks

Benefits
- Autonomy for the patient
- Bridges the gap between closure of the pivotal clinical trial and approval of drug
- Fosters development of additional uses of a drug

Risks
- Unknown risks associated; little info
- Unknown efficacy
- May adversely effect clinical trial accrual

Ways to Mitigate Risk of EAPs
- Ensure that pivotal trials are completed prior to opening EAP
- Risk of access to investigational drug for patient is carefully weighed by treating physician and FDA reviewer
Requirements for Individual Patient EAPs (21 CFR 312.310)
• Treating physician determines probable risk from drug not > than that from disease
• FDA determines that patient can’t obtain access to drug from another type of IND
• FDA requires reporting
• FDA may request consolidation of multiple cases into a single, intermediate sized IND

Requirements for Treatment IND or Protocol (21 CFR 312.320)
• Drug is being investigated in clinical trial designed to support marketing OR trials are complete
• Company is actively pursuing marketing approval
• Sufficient evidence of safety and effectiveness
• Additional safeguards
  – Monitoring

Single Patient INDs
Implementing the Process
Five Components
1. Patient-urgent need, limited info, costs?
2. Doctor-initiates process, contacts company, monitoring and reporting
3. Manufacturer-must be willing to provide drug
4. FDA-Resource intensive, assesses data, confirms patient protections in place
5. IRB-May not be familiar with procedure, may overestimate risk, requires full review
What Information Do I Send to Get a Single Patient IND?

1. Statement that this is a request for Individual Patient IND for treatment use
2. Brief clinical history of the patient including: Diagnosis, disease status, prior therapy, response to prior therapy, rationale for requesting the proposed treatment
3. Proposed Treatment Plan
4. Chemistry/Manufacturing/Controls & Pharmacology/Toxicology Info requirement may be met by Letter of Authorization from Drug company.
5. Informed consent statement
6. Investigator qualification statement
7. FDA Form 1571
8. Contact Information for Requestor

Send to FDA review division that handles disease/drug (DHP, DOP1, or DOP2). See contact #s on last slide.

Emergency INDs

- Request via phone (see #s on last slide)
- Shipment and treatment may occur after verbal approval
- Written information must follow

Abbreviations

- FDA-Food and Drug Administration
- IND-Investigational New Drug Application
- NDA-New Drug Application
- BLA-Biologic License Application
- EAP-Expanded Access Programs
- IRB-Institutional Review Board
- PMR-Post Marketing Requirement
Resources

• Expanded Access:
  http://www.fda.gov/forpatients/other/expandedaccess/default.htm

Office of Hematology Oncology Products Contact #s

<table>
<thead>
<tr>
<th>CDER Review Division</th>
<th>Telephone Number</th>
<th>FAX Number</th>
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<tbody>
<tr>
<td>Division of Oncology Products 1</td>
<td>301-796-2330</td>
<td>301-796-9883</td>
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<tr>
<td>Division of Oncology Products 2</td>
<td>301-796-2320</td>
<td>301-796-9849</td>
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