THE FDA, THE DRUG APPROVAL PROCESS, AND THE PATIENT VOICE

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Goals of Today’s Presentation

• Explain FDA’s role in the review of new drugs and the key steps in the process
• Describe the increasing importance of the patient voice at the FDA, as well as “entry points” where advocates can be particularly influential
• Discuss ways in which all stakeholders in drug development can work together for the benefit of patients
How FDA Approves New Drugs

• To market a prescription drug in the United States, a manufacturer requires approval from the FDA
  – Must demonstrate the drug’s safety and effectiveness
  – Must ensure that manufacturing plant passes inspection
  – Must obtain approval for all written material about the drug, also known as “labeling”
Standard Process of Drug Approval

Source: Congressional Research Service Report for Congress, July 2012
IND Application

• Before testing in humans (clinical testing) the drug’s sponsor must submit an **Investigational New Drug (IND)** application to the FDA
  – IND includes information about the proposed clinical study design, completed animal test data, and the lead investigator’s qualifications
  – Application must include an “Indication for Use” section describing what the drug does, the clinical condition and intended population
  – Must include the written approval of an Institutional Review Board (IRB)
IND Application

- FDA has 30 days to review an IND application
- Unless FDA objects, a manufacturer may then begin clinical testing
- Focus of IND review: safety
Clinical Trials

• Once an IND has been approved, researchers can begin clinical trials
  – Phase I: Small number of volunteers to determine dosing and identify side effects
  – Phase II-III: Larger number of individuals with particular characteristic, condition, or disease of interest to gather evidence of the drug’s efficacy, effectiveness, and safety
Submission of Marketing Application

• Once a manufacturer completes the clinical trials (usually takes 3 to 7 years), it submits the marketing application to FDA
  – These applications contain not only the clinical trial results, but also information about the manufacturing process and facilities, including quality control procedures
Marketing Application Content

• The applications include:
  – Product description
  – Indication
  – Labeling
  – Manufacturing description
FDA Review

• FDA considers three primary questions in its review of applications:
  – Whether the drug is safe and effective in its proposed use and whether the benefits of the drug outweigh the risks ("substantial evidence of safety and effectiveness");
  – Whether the drug’s proposed labeling is appropriate, and what it should contain;
  – Whether the methods used to manufacture the drug and the controls used to maintain the drug’s quality are adequate
FDA Review Team

- Multidisciplinary group including representatives from:
  - Clinical
  - Chemistry, Manufacturing, and Controls
  - Pharmacology
  - Statistics
  - Pharmacology
NDA/BLA Review Timeline

FDA Decision

• **Approval**: may include specific conditions, such as required post-approval studies, restrictions on distribution, or required labeling disclosures.

• **Major amendment**: extension of review clock (typically by 3 months) for applicant to address ongoing questions/issues.

• **Complete response**: aka “rejection” – FDA sends letter to applicant describing specific deficiencies and recommending ways to make the application viable, as appropriate.
Post-Approval Procedures

• FDA’s role in ensuring a drug’s safety and efficacy continues after approval (*postmarket regulatory procedures*)
  – Companies must report all serious and unexpected adverse reactions (clinicians and patients may do so as well)
  – FDA oversees surveillance, studies, labeling changes, and information dissemination
The Voice of the Patient at FDA

*Image source: JDRF/University of Colorado-Anschutz*
Why Should FDA Value Patient Input?

- Patients who live with a disease have a direct stake in drug review process and are in a unique position to contribute to drug development.
- FDA reviewers could benefit from systematic approach to obtaining patient perspective on disease severity or unmet medical need.
- Recent legislation empowers patients in the drug development process more than ever.
Recent Patient-Focused Legislation

- Food and Drug Administration Safety and Innovation Act (FDASIA) signed into law in July, 2012
  - Section 1137 contains specific language aimed at:
    - Developing and implementing strategies to solicit the views of patients during the drug development process
    - Consider patient perspectives during regulatory discussions
- Upcoming reauthorization of the Prescription Drug User Fee Act (PDUFA VI) will MAY include statutes to further strengthen patient voice at the FDA
Post-FDASIA Role of Patients in Drug Development and Review
FDA: Points of Entry for Patients

- **Before and during clinical trials:**
  - Benefit-risk assessment
  - Patient focused drug development

- **During FDA review:**
  - Patient representative program
  - Advisory committee participation
CDER’s Benefit-Risk Framework

• With FDASIA, CDER identified the need for a more structured Benefit-risk assessment in the review process to:
  – Better communicate the reasoning behind its decisions
  – Ensure the “big picture” is kept in mind during a complex, detailed review
CDER’s Benefit-Risk Framework

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<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tr>
<td>Analysis of Condition</td>
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<td>Current Treatment Options</td>
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<td>Benefit</td>
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<td>Risk</td>
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<td>Risk Management</td>
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**Benefit-Risk Summary and Assessment**
### Sample Benefit-Risk Framework for Lung Cancer: Analysis of Condition and Current Treatment Options

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| **Analysis of Condition** | - There are more than 200,000 new cases and ~160,000 deaths from lung cancer every year.  
- Prognosis depends on the type and stage of lung cancer. The average 5-year survival rate for NSCLC is ~15%. Over 50% of patients are diagnosed at an advanced stage, once the cancer has spread (metastasized) to the brain, bones, and other areas.  
- Patients in early stages of lung cancer may not experience any symptoms. When symptoms do appear, they can include shortness of breath or difficulty breathing, coughing, coughing up blood, pain, weight loss, and fatigue.  
- Lung cancer and its treatment can have a significant impact on patients’ ability to manage work and family life and their overall quality of life. Many patients live with uncertainty, fear, anxiety, and depression.  
- See the *Voice of the Patient* report for a more detailed description of patients’ perspectives on lung cancer symptoms and impacts. | Lung cancer is a serious and life-threatening disease. It remains the leading cause of cancer deaths in the United States. It is a rapidly fatal disease, and prognosis is dismal. While symptoms vary depending on the type and stage of lung cancer, the disease and its treatment can have a debilitating effect on patients’ lives. |
| **Current Treatment Options** | - The standard of care depends on the type and stage of the cancer. In early stages, surgery in combination with radiation therapy and/or chemotherapy can potentially be curative. In later stages, these treatments may be used to shrink or slow tumor progression or prolong life.  
- FDA-approved chemotherapy treatments include cisplatin, paclitaxel, gemcitabine, docetaxel, pemetrexed, and others.  
- Molecularly-targeted therapies are aimed at treating patients with specific genetic changes. FDA-approved targeted therapies include crizotinib, erlotinib, and afatinib.  
- Patients can develop resistance to chemotherapy and targeted therapies drugs after extended use, making some treatments less effective over time.  
- Side effects and risks vary depending on the type of treatment and can have a significant impact on patients’ quality of life. Side effects of chemotherapy may include fatigue, nausea, nerve damage, cognitive impairment, hair loss, and increased risk of infection or bleeding. Side effects of targeted therapies may include rash, diarrhea, fatigue, high blood pressure, increased risk of bleeding, visual changes, lung injury, and liver injury.  
- Palliative or supportive care therapies include supplemental oxygen, pain medications, steroids, and non drug therapies such as breathing exercises and relaxation techniques.  
- See the *Voice of the Patient* report for a more detailed description of patients’ perspectives on lung cancer treatments and treatment decision making. | There is a continuing need for additional treatment options for lung cancer patients. While some effective treatments exist, they can only be potentially curative if the disease is diagnosed in early stages. Most treatments are toxic and their side effects can have a significant impact on patients’ daily lives. Emerging targeted therapies are promising for subsets of lung cancer patients.  
The potential development of resistance to chemotherapy or targeted therapies further supports the need for an expanded treatment armamentarium.  
Patients’ treatment decisions often require making difficult tradeoffs between increasing the chance to prolong life and preserving quality of life. |
B-R Assessment in FDA Review

Use of Benefit-Risk Assessment Framework in drug review
From Benefit-Risk to PFDD

• Patients are uniquely positioned to help FDA understand the therapeutic context
  – Current mechanisms for obtaining patient input are often limited to discussions related to specific applications under review

• **Patient Focused Drug Development (PFDD)** is an FDA commitment under FDASIA
  – CDER and CBER will convene at least 20 meetings on specific disease areas FY2013-2017 (19 already)
  – Meetings can help advance systematic approach to gathering input
Identifying Disease Areas: Criteria

- Disease areas that:
  - Are chronic, symptomatic, and affect functioning and ADLs
  - Have aspects that are not captured in clinical trials
  - Have no or few therapies, or available therapies do not affect how a patient feels, functions, or survives
  - Reflect a broad range of severity and affected populations
Meeting Format

• Meetings follow similar, but tailored design
  – Take into account current state of drug development, specific interests of review divisions, needs of patient population

• Discussion elicits patients’ perspectives on their disease and treatment approaches

• Input is gathered in multiple ways
  – Patient panel input and discussion with audience
  – Interactive webcast and teleconference
  – Polling questions to aid meeting discussion
  – Federal docket to allow for more detailed comments
Samples of What FDA Asks

• Which symptoms have the most significant impact on your daily life?... On your ability to do specific activities?

• How well does your current treatment regimen treat the most significant symptoms of your disease?

• What specific things would you look for in an ideal treatment for your condition?

• What factors do you take into account when making decisions about using treatments? .... Deciding whether to participate in a clinical trial?
# Participation Estimates

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<tr>
<th>In-Person</th>
<th>Registered</th>
<th>Attended</th>
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<tbody>
<tr>
<td>Patient / Representatives</td>
<td>40 – 185</td>
<td>30 - 75</td>
</tr>
<tr>
<td>Other (e.g., NIH, industry)</td>
<td>40 – 115</td>
<td>30 - 70</td>
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<tr>
<td><strong>Webcast</strong></td>
<td>250 - 650</td>
<td>~50%</td>
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<tr>
<td><strong>Docket Submissions</strong></td>
<td>15 - 400</td>
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Preliminary Findings

• Patients with chronic serious disease are the real experts on what it’s like to live with their condition

• For progressive degenerative diseases, many patients/parents feel an ideal treatment would at minimum stop progression of loss of function

• Patients “chief complaints” may not be factored explicitly into drug development plans, including measures of drug benefit planned in trials
Preliminary Findings

• Patients want to be as active as possible in the work to develop and evaluate new treatments
  – They want their experience described using words that they consider to best describe how it feels

• They and their caregivers are able and willing to engage via the Internet, social media, and all other means at their disposal

• They don’t expect FDA to address all the gaps in current treatment/approaches to drug development but do want FDA to help identify the most effective pathways for them to play major contributing role
Potential PFDD Outcomes

• Each meeting results in a “Voice of the Patient” report that captures patient input
  – Summarizes participants’ experiences and perspectives, in their own voices
  – Meeting input may be incorporated into the benefit-risk framework

• This input can help FDA staff to:
  – Conduct benefit-risk assessments for other products under review
  – Advise sponsors on their development programs
Potential PFDD Outcomes

• Input could support drug development more broadly:
  – Help identify specific areas of unmet need in patient population
  – Stimulate longer-range development of new patient-focused outcome measures
  – Incorporate the voice of the patient earlier in drug development programs
Potential PFDD Outcomes

- **Basic Research/Discovery**
  - PRO tool development and qualification

- **Translational**
  - IND

- **Clinical**
  - NDA/BLA

- **Post-marketing**
  - Patients identify important dimensions of benefit not adequately captured in current studies; need for PRO tool(s)
  - Patient input on effectiveness & tolerability of currently available therapy (unmet medical need)

- **FDA**
Externally-led “PFDD Meetings”

• There has been interest in expanded efforts to gather patient input in support of drug development and evaluation

• Meetings conducted by patients and their advocates provide an opportunity to expand the benefits of PFDD

• Mechanisms have included:
  – Public meetings conducted within D.C. area
  – Small meetings at FDA/online with patients
  – Patient surveys and/or written submissions to a public docket
Patient Representative Program

- FDA recruits **patient representatives** to provide the unique perspective of patients and family members directly affected by serious or life-threatening disease.

- Representatives bring a personal viewpoint to the process and communicate a collective patient perspective:
  - A *patient* perspective is created when a person goes through personal experience with the disease.
  - A *collective patient* perspective is created when the person has knowledge of others’ disease experiences.
Patient Representative Program

- Criteria for becoming an FDA patient representative:
  - U.S. citizen at least 18 years of age
  - Personal experience with the disease as a patient or caregiver
  - Ability to be objective while representing the concerns of other patients
  - Willingness to communicate their views
  - Knowledge about treatment options and research
  - No financial or ethical conflicts of interest
Patient Representative Program

• Serve in several ways, including:
  – On advisory committee panels, where they offer the patient perspective, ask questions, and give comments to assist the committee in making recommendations
  – As consultants for drug review
  – As presenters at FDA meetings and workshops on disease-specific or regulatory/health policy issues

• FDA conducts training for patient representatives
  – Individual “FDA 101” training
  – Monthly webinars
  – Annual workshop for newly recruited patient representatives
FDA Advisory Committees
FDA Advisory Committees

• The purpose of an **FDA Advisory Committee** is to provide the Agency with external expert advice during the review.

• Typically the FDA notifies the company no later than 74 days of receiving the application if an advisory committee will be convened.

• Typically an advisory committee is convened 8-12 weeks prior to FDA having to make a decision on whether to approve or reject an application.
FDA Advisory Committees

• May be convened if:
  1. The application is a new molecular entity (NME)
  2. The clinical trial design used novel clinical or surrogate endpoints
  3. There are significant issues regarding safety and/or effectiveness of the drug or biologic
  4. The application raises significant public health questions regarding the role of the drug or biologic in the treatment or prevention of a disease
Open Public Hearing

• Every advisory committee includes an open public hearing (OPH)
• Interested persons may present information or views orally or in writing
• Minimum of 60 minutes per meeting
  – If there is overwhelming interest, the committee chair may extend the OPH
• While there is a patient representative on the advisory committee panel, the OPH is the opportunity for broader input from patients and caregivers
Open Public Hearing Speakers

• Have a personal story to share
  – While the majority of the advisory committee meeting is devoted to evaluating scientific questions, the OPH provides an opportunity for individuals to discuss unmet medical need, to describe their risk tolerance, and describe their own experience in their own words
  – Less common for speakers to weigh in on review-related issues that have arisen over the course of sponsor and FDA presentations and advisory committee deliberations
Open Public Hearing Speakers

• A patient or caregiver can provide their personal, real life experiences and describe how their life would be impacted if the investigational product were/were not approved

• A clinical trial participant can share their experience while on the investigational drug, describing the benefits they experienced and how that compared with any adverse events

• When there is uncertainty with the science, the patient voice can help committee members better understand the key issues affecting patients
Open Public Hearing Speakers

- In addition to patients/caregivers, patient organization representatives can provide comments to support the needs of patients
  - Large “umbrella” organizations can provide context to the overall unmet need for new therapies across diseases
  - Disease-specific organizations can speak to the needs of patients and the input they have received from them
What’s Next?

Image source: NPKUA
Looking to the Future

• Patients, industry, scientists, and the FDA must work together to advance the science of patient input, discussing:
  – How to best proceed in obtaining patients’ reports, assessments, and preferences, to inform patient-centered development and benefit-risk assessment
  – Patient preferences for treatment impacts and tolerance of uncertainty about meaningful, significant potential benefits versus harms
  – Approaches to bridge from initial patient-focused meetings to more systematic collection of patients’ experience living with a particular disease
Initial Steps to Consider

1. Organizing and uniting the patient community for specific disease states
   - The patient voice is represented by a wide range of individuals and organizations
   - Representatives from the patient community (e.g., patients, caretakers, advocates, physicians) can unite to ensure that their respective voices are heard
2. Defining meaningful engagement

- Patient engagement can represent a range of activities, from passive engagement (e.g., clinical trial participation) to more active participation (e.g., research development)

- Across this spectrum of activities, the elements that constitute or can most effectively help achieve meaningful results have yet to be clearly defined
Future Goals

3. **Identifying and removing barriers to meaningful engagement**
   - Stakeholders should work together to determine which barriers exist and ways to remove them to ensure that FDA, industry, scientists, and patients can work together to better understand each others’ needs
Future Goals

4. **Promoting active, ongoing collaboration**
   - For patient engagement to move forward on a large scale, all parties must be active collaborators
   - FDA, industry and patients/advocates must work together to collect information on:
     - The impact of a disease or condition on quality of life
     - A better understanding of individual experiences with treatment regimens
     - What aspects of treatment or symptom relief are most important to patients
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THANK YOU

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