EXPANDED ACCESS TO INVESTIGATIONAL DRUGS;
BACKGROUND & ISSUES

THE LEUKEMIA & LYMPHOMA SOCIETY AND
NATIONAL ORGANIZATION FOR RARE DISORDERS
PANELISTS

• John Murphy, General Counsel, PhRMA
• Richard Klein, Director, FDA Patient Liaison Program
• Carmen Paradis, M.D., Director, Research Ethics Program, Bioethics Department, Cleveland Clinic
• Jim Shehan, J.D. Of Counsel, Hyman, Phelps & McNamara, P.C.
• Ernest S. Voyard, J.D. Senior Director of Regulatory Affairs, The Leukemia & Lymphoma Society

• Moderator: Wayne Pines, President, Regulatory Services & Healthcare, APCO Worldwide
AGENDA

• **Introductions**: Wayne Pines, APCO Worldwide
• **Legal Perspective**: Jim Shehan, Hyman, Phelps & McNamara
• **Bioethical Perspective**: Carmen Paradis, Cleveland Clinic
• **Patient Perspective**: Ernest Voyard, Leukemia & Lymphoma Society
• **Industry Perspective**: Sascha Haverfield, PhRMA
• **FDA Perspective**: Richard Klein, Office of Health & Constituent Affairs
• **Discussion**
BACKGROUND - INVESTIGATIONAL DRUGS

- The Federal Food, Drug, and Cosmetic Act ("FDC Act") gives FDA general authority to regulate investigational drugs
  - The FDC Act prohibits the use of all “unapproved new drugs”
  - But Section 505(i) exempts new drugs “intended solely for investigational use” from the prohibition
  - The exemption is conditioned upon compliance with certain FDA regulations
  - FDA has promulgated extensive regulations governing the use of investigational drugs, and the submission to, and review by, FDA of investigational new drug applications ("INDs")
  - All expanded access falls under Section 505(i) and 21 C.F.R. Part 312, the IND regulations
LEGAL HISTORY

- **Pre-1987**: No formal regulatory recognition of expanded access in FDA regulations, but, informally, it did occur.
- **1987**: FDA revised the IND regulations to authorize use under a treatment IND or treatment protocol (for relatively broad populations) if certain criteria were met.
- Single-patient use and emergency use were implicitly acknowledged but no criteria or submission requirements were provided.
• **1987-1997**: The lack of criteria for single patient use led to criticisms - inconsistent FDA policies, inequitable access and preferential access for certain categories of patients (cancer and HIV)

• **1997**: The FDA Modernization Act (FDAMA) provided a statutory basis for expanded access to investigational drugs
• **2006**: FDA proposed regulations, which were finalized in 2009 and provide the current regulatory scheme (21 C.F.R. Part 312, subpart I)

• Neither the law nor the regulations give FDA the authority to compel companies to provide expanded access
3 TYPES OF EXPANDED ACCESS

1. Individual Patient/Emergency Use
2. Intermediate-Size Patient Populations - fewer than a treatment IND/treatment protocol, but too many to continue filing single use submissions – estimated 10-100 patients
3. Treatment IND/Treatment Protocol - broader patient population

Some patients may also get access through open-label safety studies intended to characterize the safety of a drug late in the development process
1. Patient(s) has a serious or immediately life-threatening disease or condition;
2. No comparable or satisfactory alternative therapy to diagnose, monitor, or treat;
3. The potential benefits justify the potential risks and those risks are not unreasonable in the context of the disease;
4. Use will not interfere with investigations in support of marketing approval or otherwise compromise development of the drug; and
5. Amendment to existing IND ("expanded access protocol") or new IND
SPECIFIC CRITERIA - INDIVIDUAL PATIENT/COMPASSIONATE USE/EMERGENCY USE

- Risk from the drug < risk from the disease
- Drug cannot be obtained under another IND or protocol
- Treatment limited to a single course of therapy for a specific duration unless FDA otherwise authorizes
- Written report at conclusion, including AEs
- Emergency use before written submissions available
SPECIFIC CRITERIA INTERMEDIATE-SIZE PATIENT POPULATIONS

- Typical situations – drug not being developed; patients unable to participate in clinical trials; approved product no longer marketed

- Evidence of safety at the dose and duration proposed

- Preliminary clinical evidence of effectiveness or of a plausible pharmacologic effect

- Sponsors must monitor compliance with the protocol and IND investigator regulations
SPECIFIC CRITERIA - TREATMENT IND/TREATMENT PROTOCOL

- **Typical situation** – Drug is in trials, or trials have been completed, and marketing approval is diligently being sought.

- **For a serious disease or condition**, sufficient clinical evidence of safety and effectiveness, ordinarily consisting of data from Phase 3 trials, but could be compelling data from completed Phase 2 trials.

- **For an immediately life-threatening disease or condition**, a reasonable basis to conclude that the drug may be effective and would not expose patients to an unreasonable and significant risk of illness or injury, ordinarily consisting of data from Phase 2 or phase 3 trials, but could be more preliminary clinical evidence.
SUBMISSIONS SHOULD INCLUDE

- Rationale for the intended use
- Description of the patient or patient criteria
- Method of administration
- Description of the facility where drug will be administered
- Pharmacology/toxicology/chemistry, manufacturing, and controls information (usually by providing a right to reference the manufacturer’s IND)
 RESPONSIBILITIES OF INVESTIGATORS & SPONSORS

- Investigators must:
  - obtain informed consent
  - ensure Investigational Review Board ("IRB") review and approval
  - report adverse events
- Sponsors must:
  - submit IND safety reports and annual reports
  - ensure investigators are qualified to administer the drug
- There are additional sponsor- and investigator-specific requirements for single-patient, intermediate size, and treatment INDs/ treatment protocols
WHEN CAN TREATMENT BEGIN?

- **Emergency Use** – After FDA verbal authorization (report to IRB within five days of treatment start)
- **Expanded Access INDs** – After the IND goes into effect (30 days after FDA receipt or sooner) and IRB approval received
- **Expanded Access Protocols** – Individual and Intermediate Size Patient Populations – After the protocol is submitted to FDA and IRB approval received
- **Expanded Access Treatment Protocols** – 30 days after the protocol is received by FDA or on earlier FDA notification and IRB approval received
ETHICAL CONSIDERATIONS

• Impact on the scientific process

• Availability limitations can create injustices

• Unrealistic optimism may impair patients’ ability to apply information realistically when giving informed consent
THE SCIENTIFIC PROCESS

• Research’s gold standard is a randomized, blinded, placebo-controlled trial

• Unlimited access to “new” therapies outside of a trial can undermine the science

  • patients may balk at blinding/randomization
  • inadequate enrollment is a major reason for not completing trials
LIMITED AVAILABILITY & JUSTICE

• If production capacity is limited, justice mandates that first consideration for access go to those who have participated in a trial.

• If there is excess production capacity and a reasonable rationale for expanded access, how can the decision be made “fairly” about who receives the new agent?
NOVEL THERAPY REALITY

• Only 10% of investigational agents become FDA-approved

• New FDA-approved treatments are as likely to be inferior to standard treatments as they are to be superior
UNREALISTIC OPTIMISM

- A significant discrepancy between a belief in what will happen and the likelihood of that being the case
  - It is not a matter of cognition but rather of “feeling,” of “hope”
- It is a problem when the stakes are high risk
WHAT MUST BE BALANCED?

• Protection of the scientific process, the creation of good quality information for many

• Compassion for those with terrible diseases for whom there are no alternatives

• Ensuring that an expanded access process is just for those who do participate in a trial and for those who have fewer resources
HOW TO IMPROVE THE PROCESS

• Need accurate information about patient outcomes with expanded access

• Transparency in the process

• Incentives for more trials for outlier conditions, for quicker movement to trials which expand access as/if promising evidence accumulates
OUTLINE

1. The LLS Mission

2. LLS’s position on Expanded Access

3. The Patient Perspective
   a. Process for handling Expanded Access inquiries
Blood cancers cannot be prevented or detected early.

So LLS is focused on finding **cures** and ensuring **access** to quality, affordable, coordinated care.
POSITION ON EXPANDED ACCESS

LLS supports the desire of patients to have access to potentially life-saving therapies as quickly as possible, and as such, LLS advocates for pre-market access to evidence-based treatments for patients willing to take the risk.

LLS is guided by the following criteria when working with patients on expanded access:

• The patient and provider agree that this is the best course of treatment
• No alternative therapy to diagnose or treat the disease is available
• Patients are ineligible for, or unable to participate, in a clinical trial
THE PATIENT PERSPECTIVE

- Information Resource Center (IRC)
  - 1-800-955-4572
  - Clinical trial options

- Process for handling expanded access inquiries
  - Refer patients to an existing expanded access program
  - Work with industry to facilitate other expanded access opportunities
THE PATIENT PERSPECTIVE

Kethan Kumar
2001 – 2013
JOHN MURPHY

PHARMACEUTICAL RESEARCH & MANUFACTURERS OF AMERICA (PHRMA)
The Research and Development Process

Developing a new medicine takes an average of 10 to 15 years.

- **Drug Discovery**
  - 3–6 years
  - TENS OF THOUSANDS OF COMPOUNDS

- **Clinical Trials**
  - 6–7 years
  - PHASE I: 20–100
  - PHASE II: 100–500
  - PHASE III: 1,000–5,000

- **FDA Review**
  - 0.5–2 years

- **Scale-Up to Manufacturing**
  - INDEFINITE

- **Phase IV/Ongoing Research and Monitoring**

Source: PhRMA®
EXISTING U.S. PROCESS

“Expanded access, sometimes called "compassionate use," is the use of an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options”\(^1\)

- U.S. Food and Drug Administration (FDA) regulations establish three levels of expanded access programs depending on the size of the population seeking treatment use: single patient INDs, intermediate-size patient populations, and large patient populations (widespread use)

\(^1\)http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccesstoInvestigationalDrugs/ucm176098.htm
Patients may obtain an unapproved, investigational drug for treatment use if specific criteria are met:

- The patient’s physician determines that the patient has no comparable or satisfactory alternative therapy.
- The potential patient benefit justifies the potential risks of the treatment, and those risks are not unreasonable in the context of the condition being treated.
- FDA determines that there is sufficient evidence of safety and effectiveness to support use of the investigational drug.
- FDA determines that providing the investigational drug will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval, and,
- The sponsor or clinical investigator submits information sufficient to satisfy the investigational new drug (IND) requirements.
ROLE OF THE BIOPHARMACEUTICAL COMPANY

• The initial step is for a patient’s treating physician and medical staff at a biopharmaceutical company to determine whether expanded access to an investigational drug is the best possible treatment option for the individual patient.

• The biopharmaceutical company must also determine whether expanded access would negatively impact the clinical development process, e.g. whether there is a sufficient supply of the investigational drug available.

• If those conditions are met, the biopharmaceutical company or the patient’s treating physician would submit an expanded access application to the FDA.
PATIENT ADVOCACY GROUPS, INDUSTRY & FDA SHARE THE SAME GOALS

- Bring new, safe and effective medicines to patients as quickly as possible

- Identify ways to modernize the clinical trial, drug development, and FDA review processes to accelerate the availability of new medicines

- Help patients and physicians understand and navigate the full range of potential treatment options, including approved medicines, clinical trials, and expanded access, when appropriate
DEVELOPING NEW, SAFE & EFFECTIVE MEDICINES: KEY POINTS TO CONSIDER

• FDA approval remains the best way to ensure that new, safe and effective medicines are available to patients
  • Successful completion of the clinical trial process is required to demonstrate to the FDA that an investigational drug is safe and effective so that it can be made available to a broader patient population
  • Clinical trials are the primary route by which patients can participate in the drug development process, receive access to unapproved investigational drugs, and contribute to the collection of safety and efficacy data necessary for FDA approval
DEVELOPING NEW, SAFE & EFFECTIVE MEDICINES: KEY POINTS TO CONSIDER

• For patients with a serious or life-threatening disease who are ineligible or unable to participate in a clinical trial, use of an unapproved investigational drug via an expanded access program may be an option.

• Expanded access programs are part of the biopharmaceutical industry’s commitment to patients. A variety of challenges must be addressed to avoid delays in the clinical development and FDA approval of new medicines for broader patient populations.
The development of new, safe, and effective medicines for serious or life-threatening diseases represents an urgent and unique challenge that requires special attention.

Current proposals to expand usage of unapproved investigational drugs jeopardize the FDA’s critical role in the drug approval process and may undermine the essential process of investigating a drug’s safety and effectiveness in a systematic way.
MATCHING THE URGENCY OF THE U.S. REGULATORY SYSTEM TO THE URGENCY OF PATIENTS’ UNMET MEDICAL NEEDS

• Instead, patients facing serious and life-threatening diseases or conditions deserve earlier access to approved medicines that have satisfied FDA’s standards for safety and effectiveness based on early stage data sets in areas of unmet medical need.

• All stakeholders - patients, physicians, FDA, biopharmaceutical companies, academia, and policymakers at the state and federal level - must work together to optimize the federal expanded access process.
IMPLEMENTING THE PROCESS

• Involves
  • the patient
  • the doctor
  • the sponsor
  • FDA
  • IRB
FILING AN EXPANDED ACCESS REQUEST

A request for individual patient use of an investigational drug must be received by the FDA before shipment of, and treatment with the drug may begin. An Investigational New Drug application, or IND allows an unapproved drug to move in interstate commerce.
Requests for Individual Patient INDs should include the following information:

• Statement that this is a request for an individual patient IND for treatment use
• Brief Clinical History of the patient including:
  • patient’s initials, age and gender
  • patient’s diagnosis / requested indication
  • the disease status
  • response to prior therapy
PROPOSED TREATMENT PLAN

- the dose
- route of administration
- planned duration
- monitoring procedures
- modifications (e.g. dose reduction or treatment delay) for toxicity
- can include reference to a published protocol or journal article if appropriate
CHEMISTRY, MANUFACTURING & CONTROLS INFORMATION

- usually fulfilled with a **Letter of Authorization** (LOA) from commercial sponsor (manufacturer), requested by the physician to cross reference the existing commercial IND

- allows FDA to pull the information from the existing IND
PHYSICIAN’S QUALIFICATION STATEMENT

• specifies the training, experience, and licensure of the treating physician

• The first two pages of a Curriculum Vitae (CV) typically contain this information and are usually sufficient
INFORMED CONSENT STATEMENT

• certifying that informed consent and approval of the treatment use by an appropriate Institutional Review Board (IRB) will be obtained prior to initiating treatment

• in an emergency, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment
FDA FORM 1571

- acts as cover letter for distinguishing type of request

- identifies the treating physician as the “sponsor”

- available from the FDA Expanded Access Web site
CONTACT INFORMATION FOR PHYSICIAN

• Name, mailing address, telephone and FAX number

• An IND number is assigned to the application. The IND sponsor (treating physician) provides this IND number to the drug supplier, so the supplier may ship the drug to the treating physician.

• provides information necessary for FDA to contact the physician if additional details are required
DISPELLING MYTHS

- Application process is burdensome and time consuming
  - Usually less than an hour or two for preparation
- Process is too complicated
  - FDA staff available to help physicians and counsel patients
  - FDA creating a simplified form specific to single patient requests
- FDA takes weeks to months to process an application
  - Normally 2-4 day turnaround
  - Emergency requests turned around in hours
DISPELLING MYTHS

• Negative impact of adverse event data
  • Adverse events not unexpected in these patients, often related to underlying disease
  • FDA reviewers experienced in discerning adverse events relationships
  • Four decades of experience without examples

• FDA is the barrier to expanded access
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***The third and fourth reporting period is different than the first two reporting periods. The reporting period for the first 2 periods started the day the final rule went into affect. The reporting period was changed to a fiscal year to match the reporting period for other IND submission receipts.
For Further Information

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DISCUSSION

WAYNE PINES, PRESIDENT, REGULATORY SERVICES & HEALTHCARE
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