Regulatory Issues in Orphan Drug Development

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FDA Office of Orphan Products Development (OOPD)

- **Mission:** to promote development of promising products for diagnosis, treatment, and prevention of rare diseases or conditions
- **Administering the following programs:**
  - Orphan-drug designation
  - Humanitarian-use device designation
  - Orphan product grants
- **Serving as advocate for sponsors of orphan products in FDA**
OOPD’s Other Activities (between perpetual meetings...)

- Highly experienced staff
  - Providing informal regulatory and protocol advice to sponsors
  - Interacting with patient advocacy groups, medical research communities, and government agencies
  - Working with international regulatory authorities on issues related to orphan therapeutics
  - Resolving orphan-drug shortage problems
  - Referring/matching investigators with potential drug sponsors
What’s an “Orphan Drug”?  

☐ A drug intended to treat a rare disease or condition affecting less than 200,000 people in the United States (US); or  

☐ A vaccine, a preventive drug, or a diagnostic drug to be administered to less than 200,000 people in the US per year; or  

☐ A drug to treat a common disease or condition, but without reasonable expectation of profitability by sales in the US in the first 7 years*  

* 21 CFR 316.20(b)(8)
Incentives for Developing FDA-Designated Orphan Drugs

- Written recommendations from FDA on preclinical and clinical studies necessary for drug approval
- 50% tax credit for “qualified clinical testing expenses” prior to marketing approval*:
  - Unused credit carried back 1 year and forward up to 20 years against Federal income tax
  - Including foreign clinical investigation expenses if insufficient testing population in the US
- Waiver of FDA marketing application fee ($896,200 in FY07)

* Provision administered by the IRS
Incentives for Developing FDA-Designated Orphan Drugs

- **Seven-year marketing exclusivity** after approval of the drug by FDA:
  - FDA will not approve another drug containing the same active ingredient for 7 years, unless:
    - the exclusivity holder allows FDA approval of the same drug by another manufacturer, or fails to assure sufficient quantity of the drug, or
    - the follow-on drug containing the same active ingredient is shown to be **clinically superior**.

- Eligibility for FDA orphan product development (OPD) grants
FDA OPD Grant Program

- Competitively awarded grants for clinical studies of safety and effectiveness of orphan drugs, medical foods, and medical devices
- Available to domestic or foreign, public or private, nonprofit or for-profit entities, State governments, and non-HHS federal agencies
- Grant awards:
  - Up to $200,000/year for a “small” clinical trial
  - Up to $350,000/year for a larger clinical trial
  - Up to 3 years in duration (up to $1,050,000 total!)
OOPD and Duchenne Muscular Dystrophy

- OOPD has granted orphan-drug designation to 6 drugs for DMD treatment:
  - mazindol
  - oxandrolone
  - 3-[5-(2-fluoro-phenyl)-[1,2,4] oxadiazole-3-yl]-benzoic acid
  - 2’-o-methyl phosphorothiolate oligoribonucleotide
  - L-aminocarnityl-succinyl-leucyl-argininal-diethylactate
  - idebenone

- PTC Therapeutics is a recipient of an OPD grant*

* PTC124 for treatment of DMD
Guava/cucumber Juice

The juice is good for diabetes patients who has insufficient amount of urine and swollen body.

芭樂小黃瓜汁

適合尿量少和虛腫的糖尿病患者飲用。
Taste of Raspberries, Taste of Death

“Nobody but Almighty God and I can know what I have been through these past few days...six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently...that medicine which I had used for years...suddenly had become a deadly poison in its newest and most modern form, as recommended by a reputable pharmaceutical firm in Tennessee...”

Letter by Dr. A.S. Calhoun, October 22, 1937
The 1937 Elixir Sulfanilamide Incident

- In early 1937, sulfanilamide was endorsed for treating streptococcal infection.
- Harold Watkins, chief chemist of SE Massengill Company, Tennessee, formulated a raspberry-tasting “elixir” of sulfanilamide containing: 10% sulfanilamide; 72% diethylene glycol...
  - 240 gallons were manufactured.
  - The use of diethylene glycol was not divulged.
- During September and October 1937, the elixir killed 107 patients, including 34 children.
• Dr. Massengill pleaded guilty to 112 counts of misbranding, and paid a fine of $26,100.

• The chemist Watkins committed Suicide.

“It is my plea that you will take steps to prevent such sales of drugs that will take little lives and leave such suffering behind and such a bleak outlook on the future as I have tonight.”

Letter from a mother of a dead child to President Franklin D. Roosevelt
The 1938 Federal Food, Drug & Cosmetic Act

- In December 1937, Senator Royal Copeland introduced Senate Bill S. 3073 requiring manufacturers to show their drugs were safe at the proposed dose.
  - A trade journal warned that, under S. 3073, "the Food and Drug Administration would become absolute dictator, the overlord of the drug industry."

- The Bill passed unanimously.
  - Sen. Copeland died of exhaustion 4 days after the 1938 Act was signed into law by FDR.
The Thalidomide Disaster

- Thalidomide had been marketed in Europe since 1956 for “morning sickness” symptoms.

- WS Merrell Company applied for FDA marketing approval of the drug in 1960.
  - Approval was delayed due to lack of safety data.
  - Over 20,000 Americans, including 624 pregnant patients, received the drug under the guise of investigational use.

- In 1961, the drug was pulled off the German market because of its teratogenic effects
  - Over 10,000 deformed children were born…
The 1962 Kefauver-Harris Amendments

- Spurred by the thalidomide tragedy, Congress passed the long-stalled Kefauver-Harris Amendments.
  - The amendments became law on October 10, 1962.

- The drug approval process was radically altered:
  - Manufacturers henceforth had to prove their drugs were safe and effective before they can go on the market.
The Risk-Benefit Assessment

- Basic tenets of FDA drug evaluation:
  - A drug is **safe** when the **expected therapeutic gain justifies the risk** entailed by its use.
  - A drug is **effective** if it is shown, by objective indices, to prolong life, improve physical condition, or reduce pain.
  - Determination of safety is inseparable from consideration of the drug’s effectiveness, i.e., no drug is safe unless it is effective.
- Clinical trials can go forward if the expected benefits sufficiently outweigh the expected risks.
"I believe I have a new approach to psychotherapy, but, like everything else, the FDA tells me it first has to be tested on mice."
Statutory Requirement for Showing Drug Effectiveness

☐ The standard for effectiveness is defined in the Federal Food, Drug, & Cosmetic Act as:

“…substantial evidence…consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved...that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling…”

* FDCA § 505(d)
FDA’s Current View on “Substantial Evidence of Effectiveness”

- "Gold Standard": confirmed by at least two independent adequate and well-controlled clinical studies

- Alternative standard*: one adequate and well-controlled clinical study, if:
  - the study provides robust, statistically persuasive and clinically meaningful drug effect on mortality, irreversible morbidity, or prevention of a serious disease; or
  - the drug’s effectiveness can be extrapolated from or supported by existing related studies.

* FDAMA, section 115(a)
Elements of an “Adequate and Well-Controlled Study”*

- Clear objectives and description of the study protocol

- Adequate design to permit a valid comparison with a control (i.e., placebo, dose-comparison, no treatment, active treatment, historical control) to quantitatively assess drug effect

- Adequate measures to minimize bias
  - Blinding a study to ensure assessments not influenced by knowledge of treatment assignment
  - Randomizing to avoid differences between study groups

*21 CFR 314.126
Elements of an “Adequate and Well-Controlled Study”

- Adequate selection of patients
- Well-defined, reliable, and sensitive methods for assessing treatment response
- Clear proposal of methods of data analysis
- Caveat:
  - Waiver, whole or in part, of adequate and well-controlled studies may be granted under exceptional circumstances.
  - Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the claims of effectiveness.
Need for a Control Group in a Clinical Trial

- To allow discrimination of patient outcomes (positive or negative) caused by the test drug from outcomes caused by other factors
  - Understandable **reluctance** to do controlled trials
    - When no treatment option is available
    - When the test drug is potentially “promising”
  - **Irresponsible** or **unethical** to carry out clinical trials that have no realistic chance of showing a **credible** drug effect
  - Easier to do a controlled trial before there is an **impression** that the test drug is effective!
Choice of a Control Group

- **External control group** (e.g., historical control)
  - When the disease course is predictable
  - When the drug effect is known or predictable

- **Concurrent control group** (e.g., placebo control)
  - When the disease course is unpredictable
  - When it is not possible to know or to predict the drug effect with accuracy and certainty
Types of External Control Group

- **Historical-control group**
  - A group of patients treated at an earlier time, or
  - A general medical knowledge of the disease outcome
    - Treacherous since general impressions are often inaccurate!

- **Contemporary-control group**
  - A group of patients treated at another setting

- **Baseline-control group**
  - Patients’ status on treatment compared with status before treatment
Types of Concurrent Control Group

☐ No-treatment control group
- When unfeasible to “blind” the test drug
- Possible to have an evaluator “blinded” to treatment assignment

☐ Active-treatment control group
- To show the test drug is as good as or better than a known active drug

☐ Dose-response control group
- Studying several different doses of the test drug
- May include a placebo or active treatment group
  - To avoid problem when all doses of the test drug produce similar effects!
Types of Concurrent Control Group

- Placebo-control group
  - Strong ability to minimize bias
  - Control for potential influences (e.g., other therapy, spontaneous changes in disease course, biased/subjective outcome assessments, etc.)
  - Control for the “placebo effect”
    - An average 32% of patients responded to placebo!*
  - Best way to delineate a drug’s safety profile
  - Contrary to popular belief, FDA requires placebo-control trials only when necessary!

Placebo-Control Trial

☐ When is it ethical?

- When no effective treatment is available
- Even when a proven treatment is available*:
  - investigation is for a minor condition, or
  - the use of placebo would not subject patients to additional risk of serious and irreversible harm.

☐ May be modified to resolve ethical issue

- Add-on study, replacement study
- Limited placebo period, randomized withdrawal
- “Early escape” provision, rescue treatment

* Declaration of Helsinki (2002)
“Endpoints” of a Clinical Trial

- “Traditional” endpoints: measuring the drug effects on survival, irreversible morbidity, or prevention of a disease
- “Surrogate” endpoints for accelerated drug approval purposes:
  - Laboratory or clinical measurements that are “reasonably likely” to predict clinical benefit*
  - Subject to further study to verify the drug’s benefit
- Choice of endpoints is based on the disease, patient population, study objectives, etc.

* “Reasonably likely” is a matter of (FDA) judgment!
“Accelerated Approval” of a Drug*

- Conditional approval of a drug with “meaningful therapeutic benefit” over existing treatments for serious or life-threatening illnesses
- FDA approval is based on adequate and well-controlled studies showing drug effect on:
  - a surrogate endpoint that can reasonably predict clinical benefit, or
  - a clinical endpoint other than survival, irreversible morbidity, or prevention
- Full approval is conditioned on post-marketing studies to verify clinical benefit.

* 21 CFR 314.510
Can a Drug Be Approved Early in the Development Process?

- Known as “Subpart E drugs”*
  - Expedited approval of drugs intended to treat life-threatening and severely-debilitating illnesses
  - No satisfactory alternative therapy
- Decision on marketing approvability is based on Phase 2 clinical data.
  - Usually involving Advisory Committee input
- Time to approval is 3.3 years shorter on average for Subpart E drugs†
- Relevant to many “orphan” drugs

* 21 CFR 312.84 †Tufts CSDD Approved NCE Database (2000)
“Compassionate Use” (Early Access) of an Unapproved Drug*

- An unapproved drug may be made available to patients with a serious or immediately life-threatening illness (who are not enrolled in a clinical trial), if:
  - no satisfactory alternative therapy exists;
  - the drug is being studied with due diligence, or all clinical trials are nearly completed; and
  - there is adequate evidence of the drug’s safety and effectiveness.
  - the drug would not expose these patients to unreasonable and significant additional risks.

* 21 CFR 312.34 (Treatment use of an investigational new drug)
## Drug Discovery, Development, and Approval Process

### Drug Discovery, Preclinical Testing
- **Year**: 6.5
- **Test Population**: Laboratory and animal studies
- **Purpose**: Assess safety, biological activity, and formulations
- **Success Rate**: 5000 compounds evaluated
- **Cost**: $1-12 million

### Phase 1
- **Test Population**: 20-100 healthy volunteers
- **Purpose**: Determine safety and dosage

### Phase 2
- **Test Population**: 100-500 patient volunteers
- **Purpose**: Evaluate optimal dosage, safety and effectiveness

### Phase 3
- **Test Population**: 1000-5000 patient volunteers
- **Purpose**: Confirm safety and effectiveness of long-term use

### FDA
- **Phase 4**
- **Time**: 14.5 years total – Average cost: $359 million
- **Additional post-marketing testing**
- **File NDA/BLA with FDA**: Review and approval
- **1 approved**
- **Over $900,000**

**Source:** Pharmaceutical Research and Manufacturers of America & 1993 Congressional Office of Technology Assessment
Overlapping Phases of Drug Development

- **Phase 1 trial(s)**
- **Animal efficacy testing, short-term and long-term animal safety testing**
- **File IND with FDA**
- **Phase 2 trial(s)**
- **Phase 3 trial(s)**
- **File NDA/BLA with FDA**
- **Phase 4 trial(s)**
- **Marketing approval & sales**
- **“Compassionate” use**

**“PRECLINICAL” INVESTIGATION**

**CLINICAL INVESTIGATION**

**POST-MARKETING**
I don’t know nothing about it. I don’t know nothing about it. And if I know anything about it, I can’t tell you. So, Any question?