Day one-presentation-session III
Toigo, Theresa

Regulation & other governmental influences on clinical research

Toigo, Theresa

This presentation will focus on some of the provisions included in the most recent revision to the FD&C Act, i.e., the 2007 Food and Drug Administration Amendments Act (FDAAA), including Risk Evaluation and Mitigation Strategies (REMS) and Clinical Trials Registries and Results Databases (ClinicalTrials.gov); discuss the Sentinel Initiative; review some examples of existing registries for drugs and devices; and provide an overview of the Orphan Drug Act and the Orphan Products Grant program administered by FDA.
Uniting Rare Diseases

Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories and Clinical Data

Session III
Clinical Research, Patient Care and Disease Management:

Regulatory and Other Governmental Influences on Clinical Research

Theresa Toigo, RPh, MBA
Director, Office of Special Health Issues
Food and Drug Administration
Goals

• Topics to Address
  ❖ Legal Framework
  ❖ FDA Amendments Act (FDAAA) of 2007
  ❖ Risk Evaluation and Mitigation Strategies (REMS)
  ❖ Post-marketing requirements (PMR)
  ❖ Research transparency (ClinicalTrials.gov)
  ❖ Other “registry” examples
  ❖ Orphan drug designation

• With 15 minutes to cover multiple FDA legal and regulatory topics, none of which can be covered in 15 minutes, the goal of this presentation is to raise awareness about FDA topics and show you where to find more detailed information.
Legal Framework

- Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Code of Federal Regulations (CFR)
- Guidance
Regulatory Influences on Clinical Research

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm
Regulatory Influences on Clinical Research

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm
Some Recent Changes in the Regulatory & Legal Frameworks

• The most recent revision to the FD&C Act is the 2007 Food and Drug Administration Amendments Act (FDAAA) provides FDA with additional requirements, authorities, and resources with regard to both pre- and postmarket drug safety.
  - **Title IX** gives FDA authority to require postmarket studies and clinical trials, safety labeling changes, and Risk Evaluation and Mitigation Strategies (REMS).
  - **Title VIII** provides for an expanded clinical trials registry and results database and requires greater FDA involvement in ensuring that clinical trials information is provided to the National Institutes of Health (NIH) ClinicalTrials.gov.
FDAAA Title IX- Enhanced Authorities
Postmarket Safety of Drugs

- New authorities took effect March 25, 2008.
- As of September 14, 2009 (FDA’s Two Year Report to Congress)
  - FDA issued 74 letters with postmarketing requirements to assess safety issues.
  - FDA used its new authorities to require safety label changes 22 times. Most of the required safety label changes were invoked for classes of drugs or biologics.
  - FDA has approved 78 REMS, 59 REMS that include only a Medication Guide, and 19 that include elements other than a Medication Guide (e.g., a communication plan and/or elements to assure safe use)
- In May 2008, FDA launched the Sentinel Initiative, a long-term FDA effort to create a national electronic system for monitoring product safety.
Postmarket Safety of Drugs

http://www.fda.gov/Drugs/Drugsafety/Postmarketdrugsafetyinformationforpatientsandproviders/default.htm
Postmarket Safety of Drugs

http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm
Postmarket Safety of Drugs

Postmarket Requirements/Commitments
Postmarket Safety of Drugs

Risk Evaluation and Mitigation Strategies (REMS)
Postmarket Safety of Drugs

BLA 125268 Nplate™ (romiplostim) 
REMS Submission August 12, 2008

Amgen Inc.

BLA 125268 Nplate (romiplostim)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

- To promote informed risk-benefit decisions before initiating treatment and while patients are on treatment to ensure appropriate use of Nplate (romiplostim)
- To establish the long-term safety and safe use of Nplate (romiplostim) through periodic monitoring of all patients who receive Nplate (romiplostim) for changes in bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate, thrombotic/thromboembolic complications, hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS), and medication errors associated with serious outcomes.

4. Each patient treated with Nplate is subject to certain monitoring.

a. Safety Monitoring - Prescribers must complete a Nplate™ NEXUS Program Patient Baseline Data Form for each patient within 30 days of enrollment and a Nplate™ NEXUS Program Safety Questionnaire every six months during treatment with Nplate. The Nplate™ NEXUS Program Safety Questionnaire also requires the prescriber to authorize continued treatment with Nplate. The Nplate™ NEXUS Program Call Center will remind the Nplate prescriber when it is time to complete the questionnaires for each patient. All reported serious adverse events will be further investigated and followed by Amgen Global Safety. These forms and questionnaires can be completed and faxed to Nplate™ NEXUS Program at 1-877-NPLATE0 (1-877-675-2830), or completed over the telephone. Please see appended Nplate™ NEXUS Patient Safety Registry.

b. Patient Discontinuation - At the time the prescriber determines that a patient should be discontinued from Nplate, the Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form must be completed at the time of discontinuation and 6 months later.

Please see the following appended documents:

- Nplate™ NEXUS Program Patient Baseline Data Form
- Nplate™ NEXUS Program Safety Questionnaire
- Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-up Form
Sentinel Initiative

In May 2008, FDA launched the Sentinel Initiative, a long-term FDA effort to create a national electronic system for monitoring product safety.

The Sentinel System will enable queries of automated healthcare data systems (e.g., electronic health record systems, administrative claims databases, registries) quickly and securely for relevant product safety information.

http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm
The American College of Cardiology manages the National Cardiovascular Data Registry (NCDR). This registry collects information from institutions nationwide on factors such as patient demographics, revascularization procedures, and procedural medications. CDRH obtained registry data from April 2003-April 2004 to gather information on drug-eluting stent procedures, including the utilization of antiplatelet therapy.
The FDA’s Office of Women’s Health (OWH) maintains a Pregnancy Registry Webpage that lists all active pregnancy registries. See sample below.

http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134844.htm#what
FDAAA Title VIII- Expanded Clinical Trial Registry and Results Data Bank

- FDAMA Section 113 (1997): Mandates a registry of trials for serious or life-threatening diseases or conditions conducted under an IND
- ClinicalTrials.gov launched in February 2000
- FDAAA 801 (2007):
  - Expands the registry to require submission of a broader scope of trials and more information for each trial.
  - Creates a results database
  - Includes devices
  - Failure to comply has consequences
  - Link from registry to specified FDA & NIH results information
### ClinicalTrials.gov Statistics

**as of 01/04/2010**

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>83,540</td>
<td>100%</td>
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<tr>
<td><strong>Type of Trial</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>13,717</td>
<td>16%</td>
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<tr>
<td>Interventional</td>
<td>69,471</td>
<td>83%</td>
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<tr>
<td>– Drug &amp; Biologic</td>
<td>50,460</td>
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<tr>
<td>– Surgical Procedure</td>
<td>8,886</td>
<td></td>
</tr>
<tr>
<td>– Behavioral, Gene Transfer, Other</td>
<td>13,579</td>
<td></td>
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<tr>
<td>– Device**</td>
<td>4,995</td>
<td></td>
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<tr>
<td><strong>International Sites (171 countries)</strong></td>
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<td></td>
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<tr>
<td>US only</td>
<td>38,797</td>
<td>46%</td>
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<tr>
<td>Non-US only</td>
<td>30,161</td>
<td>36%</td>
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<td>US &amp; Non-US mixed</td>
<td>5,865</td>
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<tr>
<td>Missing</td>
<td>8,717</td>
<td>10%</td>
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</table>

*91 Expanded Access records; 261 missing Study Type

**261 applicable device clinical trials – “delayed posting”**
ClinicalTrials.gov Statistics (cont.)  
(as of 01/04/2010)

<table>
<thead>
<tr>
<th>Trials by Data Provider</th>
<th>Number</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>US Federal (including NIH)</td>
<td>19,258</td>
<td>23%</td>
</tr>
<tr>
<td>Industry</td>
<td>26,257</td>
<td>31%</td>
</tr>
<tr>
<td>University, Other</td>
<td>38,025</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>83,540</strong></td>
<td></td>
</tr>
</tbody>
</table>

User Statistics

- Page Views per month: 50 Million
- Unique Visitors per day: 65,000
ClinicalTrials.gov: Registry Record

Safety and Efficacy of Cerezyme® Infusions Every 4 Weeks Versus Every 2 Weeks in Type 1 Gaucher Disease

This study has been completed.

First Received: August 15, 2006
Last Updated: September 3, 2009

Purpose

This is a multicenter, randomized trial to compare the safety and efficacy of two dosing frequencies of Cerezyme® in patients with Gaucher Disease. Approximately 90 patients will be randomized in a 2:1 (p:q) ratio to one of two treatment arms at up to 26 study centers worldwide. Patients were receiving prior to study enrollment, however, they will be randomized to receive either their total 4-week dose in two infusions, one every 4 weeks. The randomization scheme will ensure a 2:1 balance between the every 4-week versus every 2-week infusion groups, respectively.

Condition

- Gaucher Disease, Type 1
- Cerebroside Lipidosis Syndrome
- Glucocerebroside Deficiency Disease
- Glucose-6-Phosphate Dehydrogenase Deficiency Disease
- Gaucher Disease, Non-Neurological Form

Study Type: Interventional

Sponsors and Collaborators

- Genzyme

Investigators

- Study Director: Edward Kaya, M.D., Genzyme

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00364858

Keywords provided by Genzyme:
- Type 1 Gaucher Disease
- Glucocerebroside Deficiency Disease

Additional Information:

- US FDA Approved Full Prescribing Information for Cerezyme®

No publications provided
ClinicalTrials.gov: Results Record

Safety and Efficacy of Cerezyme® Infusions Every 4 Weeks Versus Every 2 Weeks in Type 1 Gaucher Disease

This study has been completed.

Study NCT00364858 Information provided by Genzyme
First Received: August 15, 2006 Last Updated: September 3, 2009 History of Changes

Study Type: Interventionsal
Study Design: Randomized, Open Label, Uncontrolled, Parallel Assignment

Conditions:
- Gaucher Disease: Type 1
- Ceroid Lipofuscinosis Syndrome
- Glucocerebrosidase Deficiency Disease
- Glucocerebroside Beta-Glucosidase Deficiency Disease
- Gaucher Disease, Non-Neuropathic Form

Intervention: Drug: Cerezyme

Pre-Assignment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations

Eligible patients were randomized 2:1 to receive Cerezyme either once every 4 weeks (Q4) or once every 2 weeks (Q2) for 24 months. The study period was from 14 December 2001 through 01 February 2007. There were 26 centers worldwide (13 United States, 1 Canada, 6 Europe, and 1 Brazil). 26 centers randomized patients to treatment.
**ClinicalTrials.gov: Results Record**

### Participant Flow: Overall Study

<table>
<thead>
<tr>
<th></th>
<th>Q2 Cerezyme</th>
<th>Q4 Cerezyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Started</td>
<td>33</td>
<td>62</td>
</tr>
<tr>
<td>Completed</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>Not completed</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Withdrawal by Subject</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Discontinuation at baseline</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliant</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Return to Q2 regimen</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clinical baseline issue</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

### Baseline Characteristics

#### Reporting Groups

- **Q2 Cerezyme**: Patients receiving Cerezyme one infusion every 2 weeks (Q2).
- **Q4 Cerezyme**: Patients receiving Cerezyme one infusion every 4 weeks (Q4).

#### Baseline Measures

<table>
<thead>
<tr>
<th></th>
<th>Q2 Cerezyme</th>
<th>Q4 Cerezyme</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants</td>
<td>33</td>
<td>62</td>
<td>95</td>
</tr>
<tr>
<td>Age [units: years]</td>
<td>44.8 ± 17.40</td>
<td>47.8 ± 14.47</td>
<td>46.8 ± 15.53</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>34</td>
<td>47</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>28</td>
<td>48</td>
</tr>
</tbody>
</table>

### Outcome Measures

1. **Primary**: Number of Participants With Clinical Success at Month 24/Discontinuation

- **Measure Type**: Primary
- **Measure Title**: Number of Participants With Clinical Success at Month 24/Discontinuation
- **Measure Description**: Patients are considered to be a clinical success if ALL of the following are met: The patient’s hemoglobin does not fall more than 1.25g/dL for more than 3 consecutive months below the patient’s baseline value, platelet count does not fall more than 25% below the patient’s baseline value or does not fall below 80,000/mm^3, bone marrow volumes are not greater than 20% above the patient’s baseline value, evidence of bone disease progression, including no incidence of pathologic fractures, lytic lesions or avascular necrosis and has had no bone crises during the study.
- **Time Frame**: Month 24 (or at time of discontinuation)
- **Safety Issue**: No

### Adverse Events

- **Serious Adverse Events**
- **Other Adverse Events**
FDA Office of Orphan Products Development

- FDA’s Office of Orphan Products Development administers the major provisions of the Orphan Drug Act (ODA) which provide incentives for sponsors to develop products for rare diseases.
- A rare disease or condition is any disease or condition which
  a) affects less than 200,000 persons in the U.S. or
  b) affects more than 200,000 persons in the U.S. but for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such a disease or condition will be recovered from sales in the U.S. of such drug.
- The ODA has been very successful - more than 200 drugs and biological products for rare diseases have been brought to market since 1983.
Developing Products for Rare Diseases

http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/
Orphan Drug Designations

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Designation Date</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic Acid</td>
<td>05-11-2009</td>
<td>Treatment of Charcot-Marie-Tooth disease type 1A.</td>
</tr>
<tr>
<td>(+/-)-1-(3-[4-Acetyl-3-Methyl-2-Propylphenoxy]-[Propoxy])-3,4-Dihydro-2-Propyl-2H-1-Benzopyran-2-Carboxylic Acid</td>
<td>03-31-2003</td>
<td>Prevention of serious adverse events associated with vascular leak syndrome caused by Interleukin-2 therapy.</td>
</tr>
<tr>
<td>(+/-)-1-Cis-3-[4-Hydroxyphenyl]-[4-(4-Methoxyphenyl)]-3,4-Dihydro-2-Hexan-2-Cresol-7-0</td>
<td>01-10-2009</td>
<td>Treatment of pancreatic cancer.</td>
</tr>
<tr>
<td>(+/-)-1-Cis-3-[4-Hydroxyphenyl]-[4-(4-Methoxyphenyl)]-3,4-Dihydro-2-Hexan-2-Cresol-7-0</td>
<td>02-01-2008</td>
<td>Treatment of cholangiocarcinoma.</td>
</tr>
<tr>
<td>(+/-)-1-Cis-3-[4-Hydroxyphenyl]-[4-(4-Methoxyphenyl)]-3,4-Dihydro-2-Hexan-2-Cresol-7-0</td>
<td>02-01-2008</td>
<td>Treatment of Stage III through Stage IV malignant melanoma.</td>
</tr>
<tr>
<td>(3r,3r)-Octanolic Acid</td>
<td>09-17-2008</td>
<td>Treatment of Gauher disease.</td>
</tr>
<tr>
<td>(3r,3r)-6-Bromo-Alpha-[2-(Dimethylamino)Ethyl]-2-Methoxy-Alpha-[1-(Naphthyl)-Beta-Phenyl]-3-Guanylmethan</td>
<td>01-10-2005</td>
<td>Treatment of pulmonary hypertension (active disease).</td>
</tr>
<tr>
<td>(3r,3r)-1-(3-Dezaazahexahydroxanthin-9-Yl)-1,4-Dideoxy-1,4-Imino-D-Ribitol-1-Phosphate</td>
<td>08-13-2004</td>
<td>Treatment of acute lymphoblastic leukemia.</td>
</tr>
</tbody>
</table>
TO LEARN MORE ABOUT APPLYING FOR ORPHAN DRUG DESIGNATION

Summary

- FDA's regulatory activities are governed by a number of Federal laws and regulations.
- The 2007 Food and Drug Administration Amendments Act (FDAAA) provides FDA with additional requirements, authorities, and resources with regard to both pre- and postmarket drug safety.
- FDA’s Office of Orphan Products Development (OOPD) is dedicated to promoting the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.
Thank You

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