Rare Disease Workshop – Hematologic Diseases
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Outline

1. Basis for Approval (Full and Accelerated)
2. Evidentiary Standard
3. Flexibility in Regulatory Procedures
   - Accelerated Approval
   - Expanded Access
   - Different Trial Design for Different Drugs
4. Regulatory Actions with Orphan Drugs in Hematopoietic Neoplasms
5. Case Study: Imatinib for CML
Basis for New Drug Approval

• Demonstration of efficacy with acceptable safety in adequate and well-controlled studies CFR 314

• Ability to generate product labeling that
  – Defines an appropriate patient population for treatment with the drug
  – Provides adequate information to enable safe and effective use – prescribing of the drug

• Analogous rules for Biologics - BLA
NDA - Efficacy Requirement

• Regular approval
  – clinical benefit or established surrogate

• Accelerated Approval
  – must be for life-threatening condition
  – advantage to available therapy
  – uses a surrogate endpoint reasonably likely to predict clinical benefit
  – requires subsequent confirmation of benefit
Accelerated Approval

• Affect a surrogate endpoint other than mortality or irreversible morbidity (e.g. ORR or PFS)
• Surrogate endpoint must be reasonably likely to predict clinical benefit, based on epidemiologic, therapeutic, pathophysiologic, or other evidence
• Additional studies confirming clinical benefit must be completed after approval
• Restated in Food Drug And Modernization Act
Evidentiary Standard - Regulatory Challenge

• Approval standards are the same for Orphan drugs as non-Orphan drugs
• Must demonstrate substantial evidence of effectiveness/clinical benefit (21CFR 314.50)
• Regulations allow room for “flexibility”
• There are “many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards”
Evidentiary Standard - Regulatory Challenge

FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards (§314.105)
Example: Expanded Access During Completion of Pivotal Trial or Approval Process

Expanded access allows patients with life-threatening disease to access promising new drug while Phase III registration trial is being completed or NDA review is ongoing.
Example: Design of Trials for Hematopoietic Neoplasms Drug Approvals Have Evolved as Novel Drugs Emerged

During the last decade, three classes of drugs have comprised the majority of approval actions at the FDA

a. chemicals/cytotoxics (Classic)
b. tyrosine kinase inhibitors (New)
c. antibodies (New)
Introduction of Targeted Therapeutics Led to Changes in Trial Design: Endpoints

ORR was primary endpoint is 55% of TKI approvals whereas 26% of antibodies were based on response rate
Introduction of Targeted Therapeutics Led to Changes in Trial Design: Type of Trial

Phase III trials were used for over 90% of the approvals for chemicals and antibodies but during the same time, clinical trials for TKIs were split 50/50 between phase II and phase III trials.
Examples of Orphan Drugs for Hematopoietic Neoplasms Which are Orphan Diseases
Hematopoietic Neoplastic Diseases with < 200,000/yr in USA

Acute Myelogenous Leukemia (AML)
Chronic Myelogenous Leukemia (CML)
Acute Lymphocytic Lymphoma (ALL)
Chronic Lymphocytic Leukemia (CLL)
Non-Hodgkins Lymphoma (NHL)
T Cell Lymphoma (TCL)
Peripheral T Cell Lymphoma (PTCL)
Cutaneous T Cell Lymphoma (CTCL)
Multiple Myeloma
Myelodysplastic Syndrome (MDS)
Myelofibrosis (MF)
Hematological Diseases with Orphan Drugs Approved

- Acute Myelogenous Leukemia (AML)
- Chronic Myelogenous Leukemia (CML)
- Acute Lymphocytic Lymphoma (ALL)
- Chronic Lymphocytic Leukemia (CLL)
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<table>
<thead>
<tr>
<th>Disease</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>CML</td>
<td>Imatinib, Sprycel, Tasigna</td>
</tr>
<tr>
<td>AML</td>
<td>ASO₃, ATRA</td>
</tr>
<tr>
<td>MDS</td>
<td>Vidaza, Dacogen, Revlimid</td>
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<tr>
<td>ALL</td>
<td>Clolar, Sprycel, Imatinib, Oncaspar, Atriance</td>
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<tr>
<td>CLL</td>
<td>Rituximab, Campath, Azerra</td>
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<tr>
<td>Myeloma</td>
<td>Melphalan, Thalidomide, Velcade, Revlimid</td>
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<tr>
<td>NHL</td>
<td>Rituxan, Zevalin, Velcade</td>
</tr>
<tr>
<td>CTCL</td>
<td>Zolinza</td>
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<tr>
<td>PTCL</td>
<td>Folotyn</td>
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Orphan Drug Approvals Which Have Changed Practice Standards

Imatinib for CML

ATRA and ASO₃ for APML

Rituxan for CLL and NHL

Dacogen, Vidaza and Revlimid for MDS

Velcade, Melphalan, Thalidomide and Revlimid for Myeloma
Orphan Drug Approvals Provide Multiple Options for Disease Subsets

AML (Drugs work by different mechanisms)
   a. ASO₃ and ATRA for APML
   b. Imatinib for Ph+ AML

MDS (Drugs work by different mechanisms)
   a. Revlimid for 5Q- only
   b. Dacogen and Vidaza for all MDS
Orphan Drug Approvals Provide Multiple Options for Disease Subsets Continued

**NHL**
- Zolinza for Mantle Cell Lymphoma (MCL)
- Rituxan for B cell NHL CD20 positive

**ALL** (Mechanism of Action Different)
- a. Imatinib for pediatric Ph+ ALL
- b. Clolar for pediatric ALL
- c. Atriance for T-cell ALL
Case History of an Orphan Drug Hematopoietic Neoplasm: Imatinib: A Tyrosine Kinase Inhibitor for CML
CML

Annual Incidence: 1.5/100,000
Median Age: 67, 10% in age 5-20 years
Ph\(^+\) Chromosomal Translocation \{t(9;22)\}
Generates P210Bcr-Abl protein which:
  bcr activates abl through oligomerization
uncontrolled abl promotes genetic
instability and signals for proliferation and
survival
Survival without therapy (3 years)
CML

Chronic Phase: Indolent with increased circulating myeloid cell mass, splenomegaly, marrow shows <5% blasts which evolves into:

Accelerated Phase: symptoms, increased blasts (<20%, new cytogenetic changes)

Blast Crisis: blasts >20%

Therapy Pre-Imatinib: Allografts, Inf, Chemo
Imatinib

Small chemical binds to ATP binding site of Abl kinase to inhibit phosphorylation of substrates of P210Bcr-Abl

Induces CCyR in 85% of CP CML
Partial CyR at 6 months, MCyR at 12 months, CCyR at 18 months

70% CP CML patients in CCyR at 5 years
Remissions can extend to 10 years
Orphan Drug Imatinib for CML

Before Imatinib, treatments (interferon, chemotherapy, allograft) were toxic life threatening in side effects, and disruptive of the quality of life.

Imatinib has transformed disease landscape and therapy. Oral therapy with Imatinib is safer and less disruptive because it targets the abnormal signal in leukemia cells which drives the disease.
Accelerated Approval for 2\textsuperscript{nd} line after interferon for CP, AP and BC CML 2001 on basis of ORR in phase II trials

Full Approval for previously untreated CP CML on basis of phase III trial comparing Imatinib to interferon/cytarabine: stopped early due to increased TTP in the interferon/cytarabine arm
Scenario #1: Adult vs Pediatric

• Problem:
  – Larger population of adults with orphan disease
  – Smaller population of children with same disease

• Mechanism of Action – the same

• Negotiation –
  – Smaller trial in pediatric population
  – Provide justification/data why the adult data can support the pediatric data
Example of Scenario #1: CML and Imatinib-Adult vs Pediatric

For the approval of newly diagnosed chronic phase CML in adults, the pivotal trial randomized 1106 patients to 550 to Imatinib and 550 to Interferon and cytarabine in 2006. In addition, 1,234 adults with relapsed refractory CML were studied for the previously treated approval 2001.

For the approval of newly diagnosed chronic phase CML in pediatric patients, 51 pediatric patients were enrolled in a open label single arm phase II trial in 2006.
Scenario #2: Initial Orphan Approval Is Used for Approval of Rarer But Related Orphan Disease

• Problem:
  Can the initial approval for orphan disease be used to help approval process for less common but related orphan disease?

• Mechanism of Action – the same

• Negotiation –
  – Smaller trial in rarer but related disease population
  – Provide justification/data why the first approval data can help support the less common orphan disease
Scenario #2: Initial Orphan Approval Is Used for Approval of Rarer But Related Orphan Disease

In 2001 addition, 1,234 previously treated adults with relapsed refractory Ph+ CML were studied in a pivotal phase III randomized trial.

For the approval of relapsed Ph+ ALL in adult patients, the approval population consisted of 48 patients in 2005.
Scenario #3: Same Orphan Drug Used for Diseases with Different Mechanisms

• Problem
  Drug approved for one orphan disease but may be relevant for other orphan diseases which have a different mechanism (kinase)

• Regulatory Action
  Much smaller numbers of patients are required for second diseases in which the same orphan drug works by a different mechanism (kinase)
Senario #3: Same Orphan Drug (Imatinib) Used for Different Disease Mechanisms

Orphan Disease (CML Ph+) # Pts
Approval 1st line CML in adults 1,106
Relapses 2nd line CML in adults 1,234

Rarer Orphan Diseases # Pts
MDS with mutated PDGF 7
GIST(Stomach Ca) Mutated c-Kit 713
Scenario #4: Drug for Totally Different Orphan Diseases of Different Prevalence

Problem: Drug is approved for adult orphan disease for which its use may be relevant to much rarer orphan diseases which arise in different types of cells through a similar mechanism.

Approval: Approval of drug in adult orphan disease which is more prevalent required far greater numbers of patients than the approvals which occurred subsequently in time of several very rare orphan diseases.
Scenario #4: CML and Imatinib

Original Orphan Disease (Ph⁺) # Pts
Approval 1st line CML in adults 1,106
Relapses 2nd line CML in adults 1,234

Rarer Orphan Diseases # Pts
hypereosinophilic syndrome 14
dermatofibrosarcoma protuberans 12
Scenario #5: Successor Orphan Drugs To Treat Resistance to Original Orphan Drug

Imatinib established the value of targeting the ATP binding site of tryrosine dependent protein kinase

Sprycel and Tasigna show activity in Imatinib resistance CML cells

Sprycel and Tasigna show faster development of CCyR and Higher % MR
Response Patterns at 1 Year Differ with 3 Different Orphan Drugs in a Single Disease Entity (CML) Reported ASCO, 2010

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<thead>
<tr>
<th></th>
<th>Kantarjian Trial</th>
<th>Larson Trial</th>
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<tbody>
<tr>
<td>Sprycel</td>
<td>83%</td>
<td>80%</td>
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<tr>
<td>Imatinib</td>
<td>72%</td>
<td>65%</td>
</tr>
<tr>
<td>Nilotinib</td>
<td></td>
<td>69%</td>
</tr>
<tr>
<td>Imatinib</td>
<td></td>
<td>36%</td>
</tr>
</tbody>
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CyR: 83% 72% 80% 65%
MMR: 46% 28% 69% 36%
Diseases with Orphan Drugs Under Study at this Time

Acute Myelogenous Leukemia
Chronic Myelogenous Leukemia
Myelodysplastic Syndrome
Myelofibrosis
Acute Lymphocytic Leukemia
Chronic Lymphocytic Leukemia
Multiple Myeloma
Conclusions

Orphan drug approval process has had a major impact on orphan diseases in the hematopoietic neoplasms

The advent of targeted therapy has produced greater regulatory flexibility even with different disease mechanisms

As new targeted therapeutics continue to evolve, the orphan drug mechanisms may continue to grow in importance