Breakthrough Therapy

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Outline

• Expedited Programs and “new” Breakthrough Therapy Designation

• Update on BT Requests for Oncology and Hematology

• Opportunities and challenges moving forward
If considering accelerated approval, post-marketing clinical trials should be underway at the time of approval.
### Timing – When is program typically granted?

<table>
<thead>
<tr>
<th>Fast Track</th>
<th>Breakthrough</th>
<th>Priority Review</th>
<th>Accelerated Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreIND/IND</td>
<td>IND</td>
<td>Time of NDA/BLA Submission</td>
<td>End of NDA/BLA Review, but postmarketing trials should be underway</td>
</tr>
</tbody>
</table>

### Requirements for Granting the Expedited Program –
All programs are for products intended to treat a serious disease

<table>
<thead>
<tr>
<th>Nonclinical OR clinical data</th>
<th>Preliminary clinical data</th>
<th>Data from NDA/BLA submission</th>
<th>Data from NDA/BLA submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential to address unmet medical need</td>
<td>-Substantial improvement over available therapy</td>
<td>-Significant improvement in safety or effectiveness over available therapy</td>
<td>-Surrogate or intermediate clinical endpoint “reasonably likely” to predict benefit -meaningful advantage over available therapy</td>
</tr>
</tbody>
</table>

### Features of the Expedited Program

| Frequent FDA interaction, rolling review, possible priority review | All Fast Track features + intensive FDA guidance, Cross-disciplinary team leader, Senior managers, Experienced reviewers | Decreases goal for completion of NDA/BLA review by 4 months | -Use of surrogate or intermediate clinical endpoint -Subject to conducting postmarketing trials to describe/confirm benefit |
Breakthrough Therapy: Inception and Definition

• FDA Safety and Innovation Act (FDASIA)
  – Signed July 9, 2012, under Section 902

• A breakthrough therapy is a drug which is
  – Intended alone or in combination with one or more other drugs to treat a serious or life threatening disease and

  – Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects in early clinical development
The Benefits of Breakthrough Designation

• All the benefits of Fast Track Designation
  – Frequent interactions with review team
  – Eligibility for priority review
  – Eligibility for Rolling review

• **Intensive guidance** on efficient drug development

• Organizational commitment
  – Involve Senior Managers and experienced reviewers
  – Assign a cross-disciplinary project lead
Breakthrough Requests

- Must be for a specific disease indication
- Intended… to treat a serious or life threatening disease
- Oncology has received almost half of the BT therapy requests

<table>
<thead>
<tr>
<th>Total Requests</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Hematology/Oncology</td>
<td>79 (43%)</td>
</tr>
<tr>
<td>All others in CDER</td>
<td>104 (57%)</td>
</tr>
<tr>
<td>Antimicrobial Products</td>
<td>35</td>
</tr>
<tr>
<td>Renal/Neuro/Psychiatric</td>
<td>30</td>
</tr>
<tr>
<td>All Others</td>
<td>39</td>
</tr>
</tbody>
</table>

Date Range: 9/1/2012 through 8/27/2014
Requests to Center for Drug Evaluation and Research (CDER)
BT Request: Outcomes

- Approximately 1/3 of applications with decisions have been granted
- Slightly higher proportion of non-oncology BT applications have been granted

<table>
<thead>
<tr>
<th></th>
<th>Submitted*</th>
<th>Decision</th>
<th>Granted</th>
<th>Denied</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>183</td>
<td>170</td>
<td>55 (32%)</td>
<td>93 (55%)</td>
<td>22 (13%)</td>
</tr>
<tr>
<td>Non-Oncology</td>
<td>104</td>
<td>96</td>
<td>32 (33%)</td>
<td>54 (56%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Oncology/hematology</td>
<td>79</td>
<td>74</td>
<td>23 (31%)</td>
<td>39 (53%)</td>
<td>12 (16%)</td>
</tr>
</tbody>
</table>

Date Range: 9/1/2012 through 8/27/2014 in CDER
*Submitted requests with no decision were under review at the time of this analysis.
“Transformative Therapies”
Ideal Breakthrough Request in Oncology

- Adequate sample size of patients
- Markedly higher response rate relative to available therapies
- Significant tumor shrinkage with a portion achieving complete response
- Substantial duration of response
- An indication with no or few effective available therapies
- A novel mechanism, first-in-class drug
- Safety profile that is as good or better than available therapies
- Early in Development providing maximum benefit of BT Designation
Analysis of BT submissions to OHOP
For those that have been Denied:

- Inadequate magnitude of benefit
- Very small sample size
  - Preliminary clinical data, not Premature clinical data
- Post-hoc subgroup analyses for OS or PFS in randomized trials failing their primary endpoint
  - Unclear Mechanistic/biologic plausibility
  - Lack of internal consistency
- Inadequate benefit in setting of significant toxicity
Opportunities and Challenges

• Like any new program, FDA and industry will need experience with the program to identify areas for improvement.
Granting Breakthrough Therapy:

– Opportunity:
  • OHOP recommends an Informal Teleconference with FDA prior to formal submission to give a preliminary assessment to sponsor

– Challenges:
  • What is the right threshold for granting a BT designation?
  • What constitutes available therapy?
  • How late is too late? Timing of BT designation request.
Implementing Breakthrough Therapy:

– Opportunities:
  • “All Hands on Deck” for Transformative Therapies:
    – Aligns and Prioritizes Key FDA review teams (Clinical, Statistics, Manufacturing, Clinical Pharmacology, Toxicology, Inspections)
  • Optimizes communication between FDA and Sponsor

– Challenges:
  • Resource saturation for both FDA and Sponsor?
  • On what basis should we rescind a BT therapy?
  • Manufacturing timelines can be a bottleneck
References:

• Guidance for Expedited Programs: