Breakthrough Therapy

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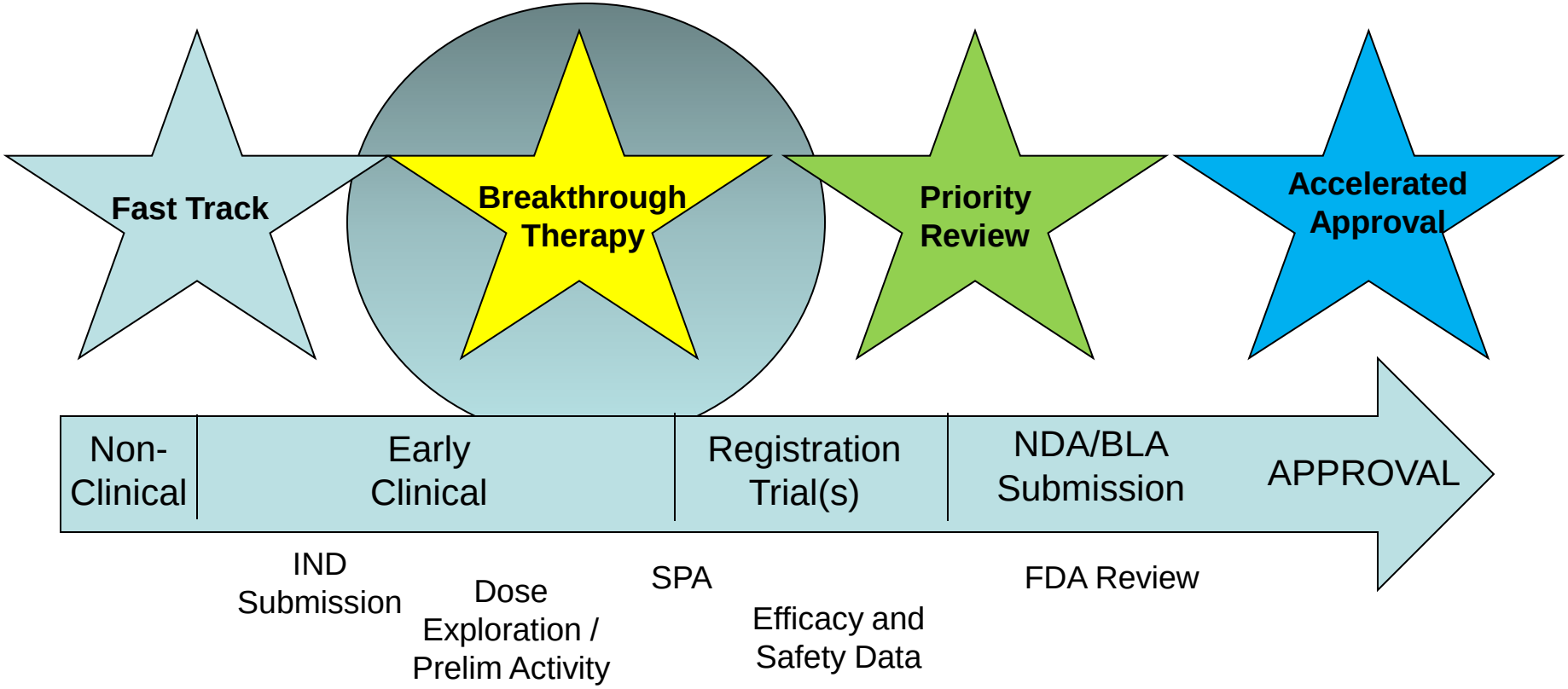
Outline

- Expedited Programs and “new” Breakthrough Therapy Designation
- Update on BT Requests for Oncology and Hematology
- Opportunities and challenges moving forward

FDA Expedited Programs



★ If considering accelerated approval, post-marketing clinical trials should be underway at the time of approval.

Fast Track	Breakthrough	Priority Review	Accelerated Approval
Timing – When is program typically granted?			
PreIND/IND	IND	Time of NDA/BLA Submission	End of NDA/BLA Review, but postmarketing trials should be underway
Requirements for Granting the Expedited Program – All programs are for products intended to treat a serious disease			
Nonclinical OR clinical data	Preliminary clinical data	Data from NDA/BLA submission	Data from NDA/BLA submission
Potential to address unmet medical need	-Substantial improvement over available therapy	-Significant improvement in safety or effectiveness over available therapy	-Surrogate or intermediate clinical endpoint "reasonably likely" to predict benefit -meaningful advantage over available therapy
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

Total Requests	**183**
Hematology/Oncology	79 (43%)
All others in CDER	104 (57%)
Antimicrobial Products	35
Renal/Neuro/Psychiatric	30
All Others	39

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

Overall	**Submitted***	**Decision**	**Granted**	**Denied**	**Withdrawn**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Non-Oncology	**Submitted***	**Decision**	**Granted**	**Denied**	**Withdrawn**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Oncology/hematology	**Submitted***	**Decision**	**Granted**	**Denied**	**Withdrawn**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

Date Range: 9/1/2012 through 8/27/2014 in CDER
*Submitted requests with no decision were under review a 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:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf