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A Peek at Drug Development Process and Endpoints in Breakthrough Therapies

Samuel Lella & Yadalam Visweswara

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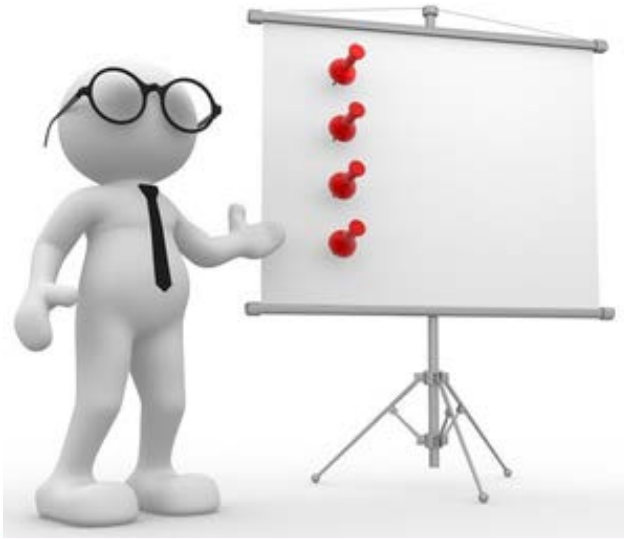
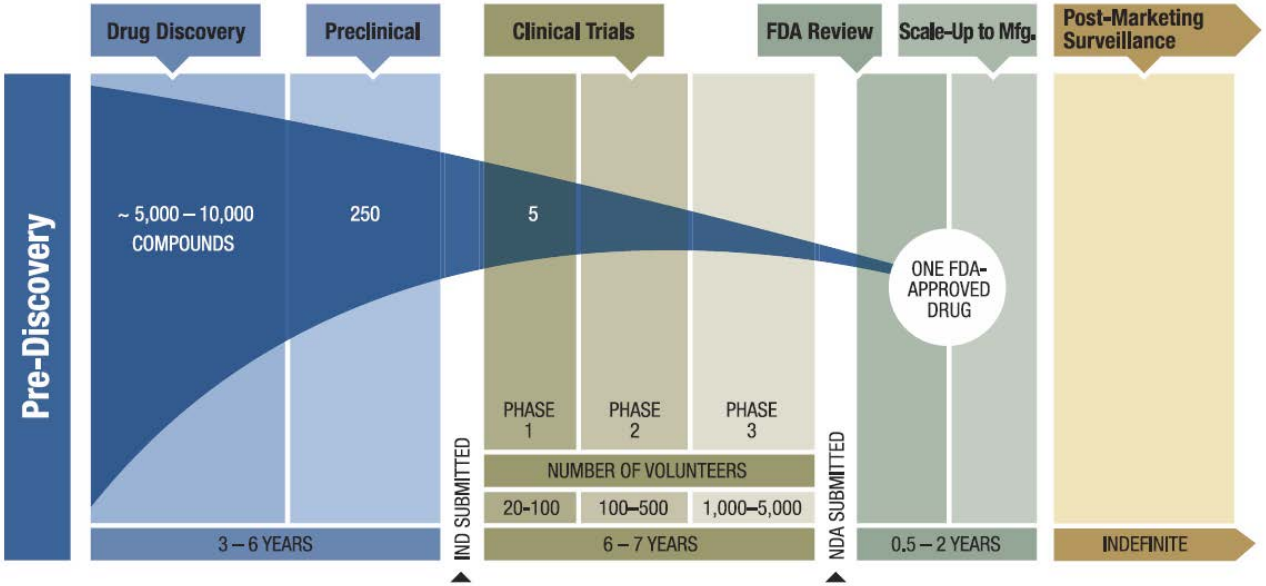
Agenda

- Introduction of Breakthrough Therapy
- Processing of Breakthrough Therapy Designation (BTD)
- BTD Vs Other fast approval processes of FDA.
- Case Studies
- Safety and Efficacy endpoints
- Q&A

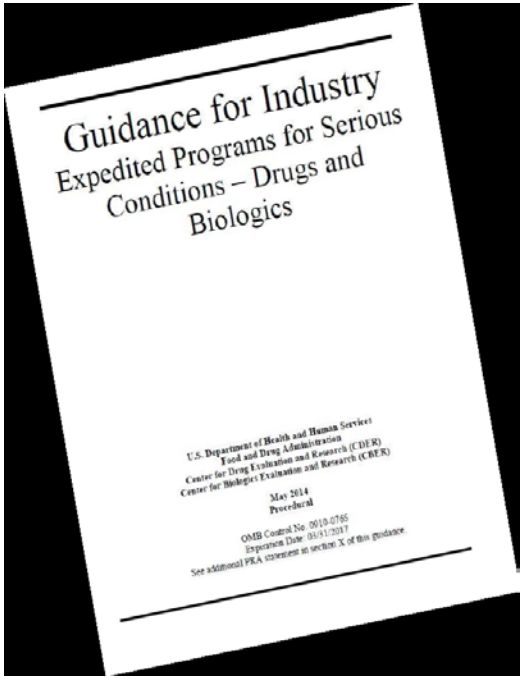


Drug Discovery and Development Timeline

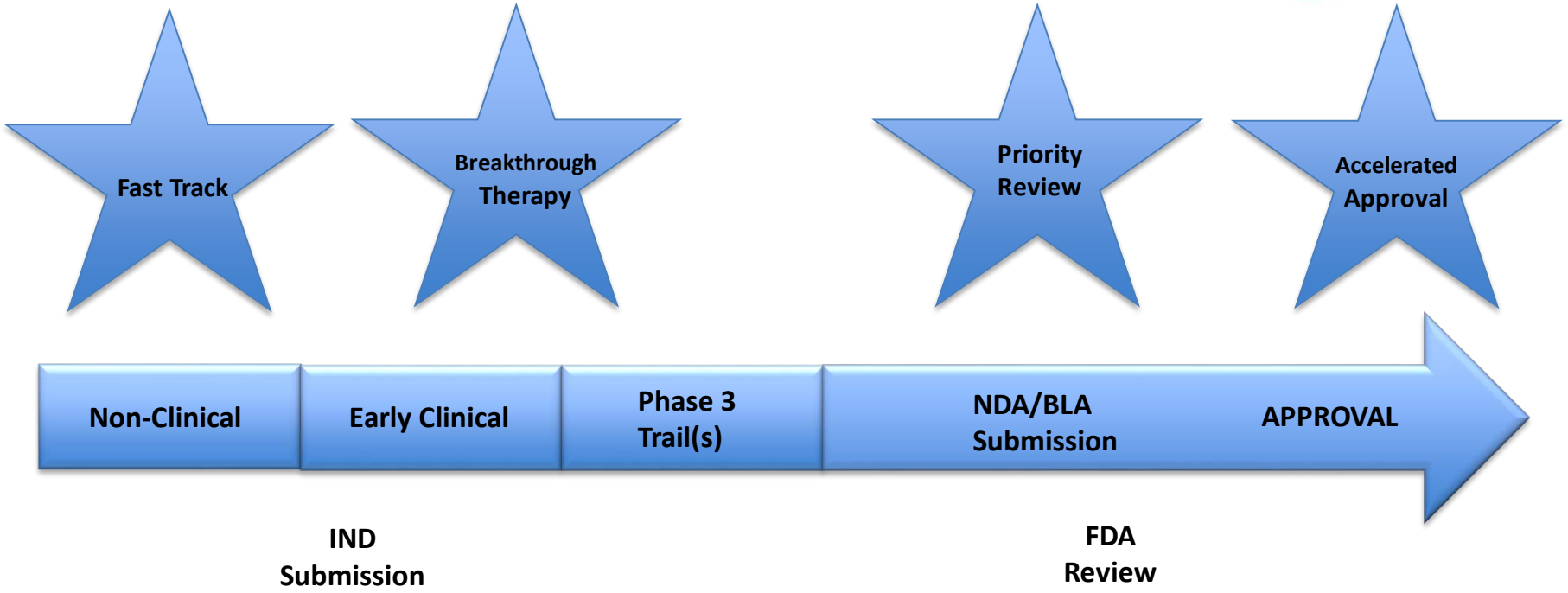


Expedited Programs

- Accelerated Approval
- Fast Track
- Priority Review
- Breakthrough Therapy



FDA Expedited Programs



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Let’s Breakthrough Serious Conditions

BT Program at a Glance

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Food and Drug Administration Safety and Innovation Act (FDASIA) was signed on July 9, 2012; this included the Breakthrough Therapy Designation

To qualify for the designation, a drug must…

- Treat a **serious** or **life threatening** disease or condition
- Provide preliminary clinical evidence indicating a **potential for substantial improvement** over existing therapies on one or more clinically significant endpoints

A drug with a Breakthrough designation will have…

- Increased communication with FDA
- FDA guidance to ensure that the design of clinical trials are as efficient as practicable
- A cross-disciplinary project lead assigned to the FDA review team and increased involvement of senior experienced review staff

FDA Approaches to Expedited Drug Development

Eligibility

BREAKTHROUGH

- Serious or life-threatening diseases
- ***Early clinical*** evidence *of* ***substantial improvement*** over existing therapies

FAST TRACK

- Broad range of serious diseases
- Potential to fill an unmet medical need

PRIORITY REVIEW

- Major advances over existing therapies

FDA Approaches to Expedited Drug Development

Designation

BREAKTHROUGH

- Can be requested by sponsor at any time after IND submission; FDA has 60 days to respond

FAST TRACK

- Requested by sponsor at any time; FDA has 60 days to respond

PRIORITY REVIEW

- Requested by sponsor at time of NDA/BLA submission; FDA has 45 days to respond

FDA Approaches to Expedited Drug Development (Contd..)

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Development & Review

BREAKTHROUGH

- **Abbreviated /condensed development**; earlier/more **frequent communication**; senior reviewers and cross-disciplinary review team
- **Review time shortened: rolling NDA/BLA data submission.**

FAST TRACK

- Earlier and more **frequent communication**
- Option for **Rolling** NDA/BLA **submission**.

PRIORITY REVIEW

- NDA/BLA data submitted in **one package**; **review time shortened** to 6 months

FDA Approaches to Expedited Drug Development (Contd..)

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Eligibility

BREAKTHROUGH

- Serious or life-threatening diseases
- ***Early clinical*** evidence *of* ***substantial improvement*** over existing therapies

ACCELERATED APPROVAL

- Serious or life-threatening diseases
- Meaningful therapeutic benefit over existing therapies
- ***Surrogate endpoint (EP)*** reasonably likely to predict clinical benefit

FDA Approaches to Expedited Drug Development (Contd..)

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Designation

BREAKTHROUGH

- Can be requested by sponsor at any time after IND submission; FDA has 60 days to respond

ACCELERATED APPROVAL

- *No formal process*

FDA Approaches to Expedited Drug Development (Contd..)

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Development & Review Process

BREAKTHROUGH

- **Abbreviated /condensed development**; earlier/more **frequent communication**; senior reviewers and cross-disciplinary review team
- **Review time shortened: rolling NDA/BLA data submission.**

ACCELERATED APPROVAL

- **Development with surrogate EP** results in conditional approval; confirmatory controlled trials with clinical benefit EP required
- **Standard 10 month review:** NDA/BLA data **submitted in one package**

Life Threatening Diseases

- Life threatening diseases are chronic, usually incurable diseases, which have the effect of considerably limiting a person's life expectancy.
- These include, cancer, diabetes, neurological conditions, coronary heart disease and HIV/Aids.

Clinical Trial Endpoints in BTD

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"... the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant **endpoints**."

Endpoint

- An endpoint is the primary outcome that is being measured by a clinical trial.
- Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumor.

Clinical Trial Endpoints- Survival Rate

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Experimental Therapy-X

Five -year survival rate of patients is higher

Placebo

Five-year survival rate of patients is lower

BTD Qualifying Criteria

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Preliminary clinical evidence

Generally derived from Phase 1 or 2 trials

Quality and Quantity Data

Ideally derived from a study comparing the drug to an available therapy or placebo with sufficient number of subjects

Preliminary clinical evidence

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Evidence to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies

Nonclinical information could support the clinical evidence of drug activity.

BTD Qualifying Criteria

Approaches to demonstrate substantial improvement

Direct comparison of the drug to available therapy shows a much greater response

The drug has an important safety advantage compared with available therapy, and has similar efficacy

Common Reasons for BTD Denial

- Evidence is too preliminary (quantity and/or quality) to be considered reliable
  - Small sample size
  - Lack of appropriate control
- Improvement over available therapy does not appear to be “substantial”
- Modification of product

Case Study 1- Eltrombopag

- Eltrombopag received FDA breakthrough treatment designation in February 2014 for patients with aplastic anemia for which immunosuppression has not been successful.[In 2017, the NIH made Eltrombopag a standard of care in aplastic anemia. It has been shown to produce a trilineage hematopoesis in some patients with aplastic anemia, resulting in increased platelet counts, along with red and white blood cell counts.

Eltrombopag-Endpoint

- After 6 weeks of therapy in a phase III trial, eltrombopag 50 mg/day was associated with a significantly higher response rate than placebo in adult patients with chronic ITP.

Case Study 2- Palbociclib

- The drug was reviewed and approved under the Food and Drug Administration's (FDA) accelerated Priority Review and Breakthrough Therapy designation programs on February 3, 2015 as a treatment (in combination with letrozole) for patients with estrogen receptor positive advanced breast cancer. This was an accelerated approval.
- In March 2017, the FDA granted regular approval to palbociclib for HER2 negative breast cancer, in combination with an aromatase inhibitor.

BTDs by Indications

Indications	Requests	Granted
Oncology	**33**	**9**
Non-Oncology	**21**	**6**
Hematology	4	3
Ophthalmology	3	1
Cardiology	3	1
Neurology	4	1
Transplantation	2	0
Nephrology, Peripheral Vascular, Burn, Hepatology	1 in each specialty	0

BTDs by Product Types

Products	Requested BTDs	Granted BTDs
Gene	26	12
Cellular	16	1
Tumor Vaccine	4	1
Oncolytic Virus	1	1

Conclusion:

Breakthrough Therapy is not granted for the benefit of Industry or the FDA; rather it is for the benefit of the **Public.**

References

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Yadalam.Visweswara
Yadalam.Visweswara@quanticate.com

Samuel.Lella
Samuel.lella@quanticate.com