FDA designations to expedite drug development

Breakthrough designations(BTD)

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Disclaimer

The views and opinions expressed in this presentation are those of the author and do not necessarily represent official policy or position of GSK or of its clients.

Agenda

- Drug and Device Development Processes
- FDA Expedited Programs
- The BTD* Request Process
  - BTD: Drug Development
  - BTD: Marketing Application Review
  - Current BTD Numbers
- Insights and experiences from BTD filing and approval
- References
- Q&A

*BTD-Break Through Designation

Drug and Device Development Processes

Step 1
Discovery/Concept

Step 2
Preclinical Research

Step 3
Clinical Research

Step 4
FDA Review

Step 5
FDA Post-Market Safety Monitoring

Discovery/Concept
Research for a new drug or device begins in the laboratory.

Preclinical Research
Drugs and devices undergo laboratory and animal testing to answer basic questions about safety.

Clinical Research
Drugs and devices are tested on people to make sure they are safe and effective.

FDA Review
FDA review teams thoroughly examine all of the submitted data related to the drug or device and make a decision to approve or not to approve it.

FDA Post-Market Safety Monitoring
FDA monitors all drug and device safety once products are available for use by the public.

FDA Expedited Programs

- *Guidance to Industry:*

  Expedited Programs for Serious Conditions – Drugs and Biologics, issued May 2014

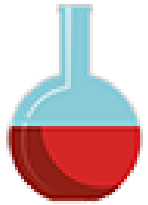
  - Single resource for information on FDA's policies & procedures
  - Describes threshold criteria applicable to conclude drug is eligibility to expedite

- **Goals**
  - To address an unmet medical need in serious or life-threatening condition
  - Intended to help ensure that therapies for these conditions are approved & available to patients as soon as it can be concluded that the therapies' benefits justify their risks
  - Allow for earlier attention to drugs that have promise in treating such conditions an expedited development & review program

FDA Expedited Programs 2

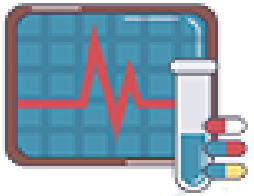
Fast Track

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.



Breakthrough Therapy

A process designed to expedite the development and review of drugs which may demonstrate **substantial** improvement over available therapy.



Accelerated Approval

These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.

Priority Review

A Priority Review designation means FDA's goal is to take action on an application within 6 months.

Fast Track

➢Criteria:

A drug that:

- Is intended to treat a serious condition **AND** nonclinical or clinical data demonstrate the potential to address unmet medical need **OR**
- That has been designated as a qualified infectious disease product

➢Features:

- FDA takes actions to expedite development and review
- Eligible for rolling review

Breakthrough Therapy Program

➢Criteria:

A drug that treats:

- Serious condition, AND
- Preliminary clinical evidence indicates that the drug may demonstrate **substantial** improvement over available therapy on one or more clinically significant endpoints

➢Features:

- Intensive guidance on efficient drug development
- Organizational commitment
- Eligible for rolling review

Accelerated Approval

➢Criteria:

A drug that:

- treats a serious condition AND
- provides meaningful advantage over available therapies AND
- demonstrates effect on surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit

➢Features:

- Approval based on an effect on surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict drug's clinical benefit

Priority Review

➢Criteria:

An application for a drug :

- That treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness

OR

- That proposes a labeling change pursuant to a report on a pediatric study under 505A OR (supplements only)
- That has been designated as a qualified infectious disease product

OR

- Submitted with a priority review voucher

➢Features:

- Shorter clock for review of marketing application compared with standard review

BTD Request Submissions

➢BTD requests (BTDRs):

Reference :Section 506(a) of the FD&C Act, as added by section 902 of FDASIA

- Can be submitted with an original IND or any time thereafter
- Ideally submitted prior to initiation of clinical trial(s) intended to serve as primary basis for demonstration of efficacy
- Must include preliminary clinical evidence
- Each indication requires a separate BTDR

*FDASIA - Food and Drug Administration Safety and Innovation Act

*FD&C - Federal Food, Drug, and Cosmetic Act. *IND- Investigational New Drug

CDER Review of BTDRs & FDASIA 902 Requirements

- 60 day review clock
- Review Division (RD) takes the lead on reviewing BTDRs
- All BTDRs also reviewed by the Medical Policy Council (MPC) to insure statutory provisions are implemented consistently
- RD makes recommendation to the MPC to grant or deny BTDR
- MPC & RD discuss & determine final BT designation

FDASIA 902 states that once a BTD granted:

Take actions to **expedite the development & review of the drug:**

- Assign a cross-disciplinary project lead **(CDPL)**
- **Hold meetings** throughout drug development
- Provide timely **advice to & interactive communication**
- Take steps to **ensure efficient clinical trial design**
- **Involve senior managers** & experienced review staff

CDER-Sponsor Meetings

➢ Initial Comprehensive Multidisciplinary BT meeting

- Type B meeting
- Ideally scheduled within 6 months of granting
- Comprehensive high-level discussion of the expedited development program
  - Planned clinical trials to generate substantial evidence to support accelerated or regular approval
  - Plans for expediting the manufacturing development strategy
  - Expanded Access programs, if applicable

➢ Subsequent Type B Meetings

- Review team continues to meet w/sponsor throughout IND phase
- Focused meetings to discuss specific development program data, milestones, and issues

➢ Critical Milestone Meetings

- Likely to take place in at earlier time points in drug development

Breakthrough Therapies

➢Drug Development Considerations

- Clinical – Trial design flexibility/innovative approaches, consideration for accelerated approval
- Product Quality –Expediting manufacturing development and novel risk mitigation strategies
- Regulatory –Potential post approval studies ,expanded access plans

➢CDER Review of BT Drug Development Programs

- Most submissions reviewed in 60 days or less
  - Limited types of submissions require 90 days
- Review staff perform periodic high-level reviews of BTD drug development programs
  - Performed approximately every 3 to 6 months

CDER = Center for Drug Evaluation and Research

Breakthrough Therapies

➢ Rescinding a BTD

Review team periodically evaluates clinical evidence

- If BTD criteria are no longer met, CDER may rescind
- Intent to Rescind letter sent to sponsor
  - Sponsor has opportunity to provide additional data & rationale and/or request a meeting
- If determined BTD criteria continue to be met:
  - Plans for development of the drug discussed & communicated to sponsor
- If determined BTD criteria no longer met:

  Designation is rescinded

➢ Advisory Committee(AC) Meetings

- AC meetings typically are not convened
  - BTD drugs generally have an acceptable:

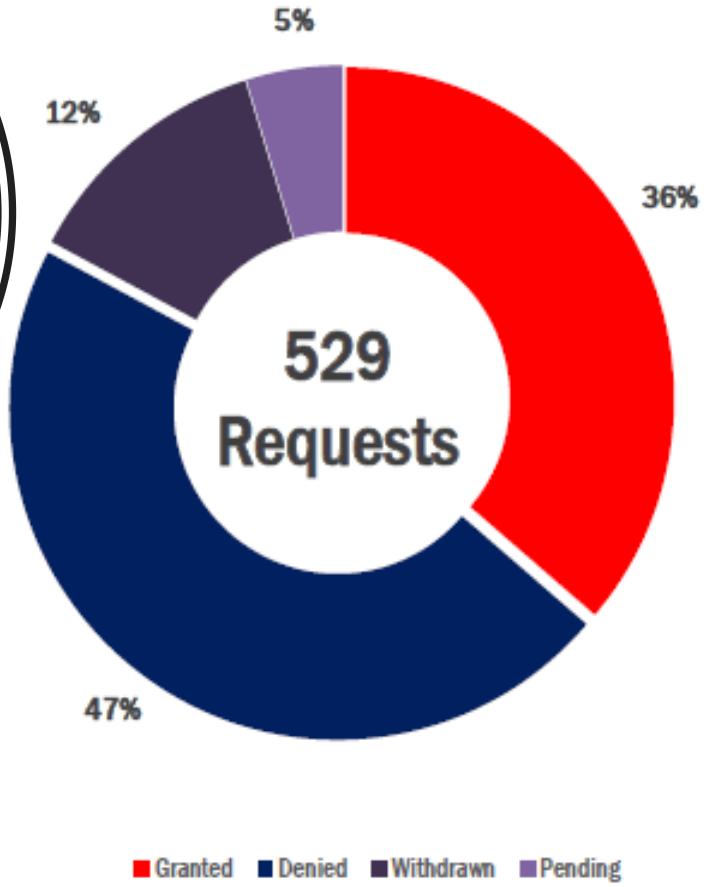
    Safety profile for indication & Clinical trial design & endpoints
  - Applications typically do not raise:

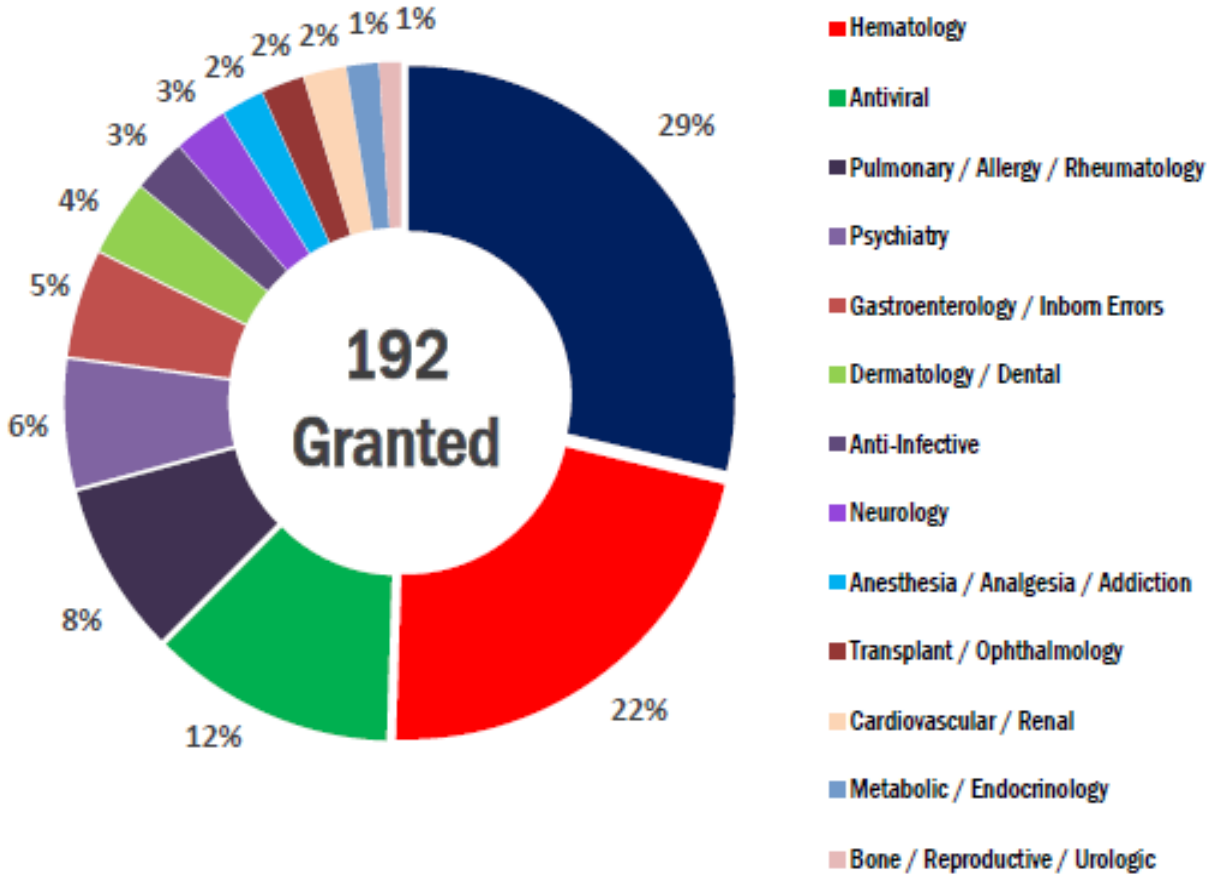
    Unexpected efficacy issues & Significant public health questions
- Need for an AC evaluated on a case-by-base basis, and may be required

CDER = Center for Drug Evaluation and Research

CDER Has Granted 192 Breakthrough Therapy Designations Since Inception

Break through Numbers





Data as of 11/30/2017

Breakthrough Numbers by year

CDER Breakthrough Therapy Designation Requests Received by Fiscal Year
Cohort: July 9, 2012* - September 30, 2017
Data as of December 31, 2017

Fiscal Year	Total Requests Received	Granted	Denied	Withdrawn
2017	111	50	49	12
2016	106	46	48	12
2015	93	32	43	18
2014	96	31	51	14
2013	92	31	52	9
2012	2	1	1	0

* Breakthrough therapy designation was enacted in the Food and Drug Administration Safety and Innovation Act on July 9, 2012.

CDER Breakthrough Therapy Designation Requests Received by Fiscal Year
Cohort: October 1, 2017 - September 30, 2018
Data as of March 31, 2018

Fiscal Year	Total Requests Received	Granted	Denied	Withdrawn
2018	64*	23	16	8

* Requests that are still pending a decision are included in the total requests received column.

Safety and efficacy in BTD trials

- Preliminary clinical evidence on safety and efficacy
- Ideally from comparator trials(either with available therapy or new drug + SOC)
- Single arm studies are also acceptable
  - Compare with well documented historical data and provides large difference
- Should have Substantial improvement on clinically significant endpoints:
  - Should be drawn from sufficient number of patients(FDA recognizes that the data cannot be expected to be definitive)
  - Approaches to demonstrate substantial improvement :

    Direct comparison with available therapy or placebo compared trials

    Well documented historical control

    Inhibits disease progression or provide safety advantage with similar efficacy

Programming Standpoints

- Go through Briefing book and understand thoroughly
- Understand data exchange standards and requirements
- Familiarize with FDA Guidance's(ex. eCTD technical guidance etc.)
- Identify and train people on eCTD requirements
- Understand company Systems & Processes
- Take adequate trainings before implementation
- Timelines – make it realistic
- Understand pooling requirements(ex. Different MedDRA ,WHODRUG versions in different studies)
- Collaboration with other line functions

*eCTD – Electronic Common Technical Document

Insights and Experiences

- Short timelines
- Less turnaround time in answering Health Authority Questions(HAQ)
- Have proper plans (Ex. plan A , B etc.)
- Thorough review and understand analysis plan
- Challenge Statistician/Clinician (ex. Redundant TFLs)
- Never simply assume - Seek clarification
- Pro-active communication
- Ensure statistical models provided in analysis plan are meaningful
- Optimal resource utilization (ex. Same person for dataset and TFL)
- Utilize best expertise (Ex. Graphs , Efficacy)
- If available, utilize different time zones(very helpful during HAQ's)
- Submit batch wise for review

References

Guidance to Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

Overview of FDA Expedited Programs with a Focus on Breakthrough Therapy

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM466480.pdf

CDER New Drugs Program:2017 Update

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM587690.pdf

About Drug and Device Approvals

https://www.fda.gov/ForPatients/Approvals/default.htm

Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review

https://www.fda.gov/ForPatients/Approvals/Fast/default.htm

Number of Breakthrough Therapy Designation Requests

https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cber&status=public&id=CBER-All-Number-of-Breakthrough-Therapy-Requests-Received-and-Approvals&fy=All

CDER BTDR's Received by Fiscal Year & Previous Cumulative FY

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/INDActivityReports/ucm373559.htm

THANK YOU

Back up slides

Serious Condition

. . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one

Drug Is Intended to Treat a Serious Condition

- A diagnostic product intended to improve diagnosis or detection of a serious condition in a way that would lead to improved outcomes
- A product intended to mitigate or prevent a serious treatment-related side effect (e.g., serious infections in patients receiving immunosuppressive therapy)
- A product intended to avoid or diminish a serious adverse event associated with available therapy for a serious condition (e.g., product that is less cardiotoxic than available cancer therapy)
- A product intended to prevent a serious condition or reduce the likelihood that the condition will progress to a more serious condition or a more advanced stage of disease

Available Therapy & Unmet Medical Need

➢Available therapy

- Is approved or licensed in the United States for the same indication being considered for the new drug and
- Is relevant to current U.S. standard of care (SOC) for the indication

➢ Unmet Medical Need

An unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population or a longer-term need for society

1. Where There Is No Available Therapy
2. Where There Is Available Therapy
3. Where the Only Available Therapy Was Approved Under the Accelerated Approval Program Based on a Surrogate Endpoint or an Intermediate Clinical Endpoint and Clinical Benefit Has Not Yet Been Verified