Breakthrough Therapy Program
U.S. Food and Drug Administration (FDA)

Presentation before the
European Commission Expert Group on
Safe and Timely Access to Medicines for Patients (STAMP)

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27 January 2015

FDA Expedited and Accelerated Drug Review Programs

- FDA has a long history of accelerated drug review programs
- These programs are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition
- The four current programs include fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation
- The next two slides include a table (minus footnotes) from FDA's "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics" available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf which describes the four programs.

FDA Expedited Drug Review Programs

Comparison of FDA's Expedited Programs for Serious Conditions

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of program	Designation	Designation	Approval Pathway	Designation
Reference	• Section 506(b) of the FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)	• Section 506(a) of the FD&C Act, as added by section 902 of FDASIA	• 21 CFR part 314, subpart H • 21 CFR part 601, subpart E • Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA	• Prescription Drug User Fee Act of 1992
Qualifying 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** • A drug that has been designated as a qualified infectious disease product[a]	• A drug that is intended to treat a serious condition **AND** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	• A drug that treats a serious condition **AND** generally provides a meaningful advantage over available therapies **AND** demonstrates an effect on a 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 (i.e., an intermediate clinical endpoint)	• An application (original or efficacy supplement) for a drug that treats a serious condition **AND,** if approved, would provide a significant improvement in safety or effectiveness **OR** • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A[b] **OR** • An application for a drug that has been designated as a qualified infectious disease product[c] **OR** • Any application or supplement for a drug submitted with a priority review voucher[d]

FDA Expedited Drug Review Programs

Comparison of FDA's Expedited Programs for Serious Conditions

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of program	Designation	Designation	Approval Pathway	Designation
When to submit request	• With IND or after • Ideally, no later than the pre-BLA or pre-NDA meeting	• With IND or after • Ideally, no later than the end-of-phase 2 meeting	• The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned endpoint as a basis for approval and discussing the confirmatory trials, which should usually be already underway at the time of approval	• With original BLA, NDA, or efficacy supplement
Timelines for FDA response	• Within 60 calendar days of receipt of the request	• Within 60 calendar days of receipt of the request	• Not specified	• Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• Shorter clock for review of marketing application (6 months compared with the 10-month standard review)[e]
Additional considerations	• Designation may be rescinded if it no longer meets the qualifying criteria for fast track[f]	• Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy[g]	• Promotional materials • Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit • Subject to expedited withdrawal	• Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

Breakthrough Therapy Designation

New designation created by the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144 (July 2012)

General Criteria

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

Assistance provided by FDA

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

Breakthrough Therapy Drug Designation Statutory Requirements

- Section 506(a) of the Federal, Food, Drug, and Cosmetic Act (FD&C Act) (added by FDASIA) provides for designation of a drug as a breakthrough therapy.
  - ". . . if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."
- The standard for breakthrough therapy designation is not the same as the standard for drug approval. The clinical evidence needed to support the designation is preliminary.
- FDA will review the full data submitted to support approval of a drug designated as breakthrough therapy to determine whether the drug is safe and effective for its intended use before it is approved for marketing.

Breakthrough Therapy Designation

- For purposes of breakthrough therapy designation, *preliminary clinical evidence* means:
  - Evidence that is sufficient to indicate that the drug may demonstrate substantial improvement in effectiveness or safety over available therapies, but in most cases is not sufficient to establish safety and effectiveness for purposes of approval.
  - FDA expects that such evidence generally would be derived from phase 1 or phase 2 trials. Nonclinical information could support the clinical evidence of drug activity.
  - In all cases, preliminary clinical evidence demonstrating that the drug may represent a substantial improvement over available therapy should involve a sufficient number of patients to be considered credible.

Breakthrough Therapy Designation

- Type of FDA assistance (as appropriate) for drugs with breakthrough therapy designation (set out in statute, section 902 FDASIA):
  - holding meetings with the sponsor and the review team throughout the development of the drug
  - providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable
  - taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment

Breakthrough Therapy Designation

- Type of FDA assistance continued:
  - assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the cross-discipline members of the review team (i.e., clinical, pharmacology-toxicology, chemistry, manufacturing and control, compliance) for coordinated internal interactions and communications with the sponsor through the review division's Regulatory Health Project Manager
  - involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review

Breakthrough Therapy Designation

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  - FDA expects that such evidence generally would be derived from phase 1 or phase 2 trials. Nonclinical information could support the clinical evidence of drug activity.
  - In all cases, preliminary clinical evidence demonstrating that the drug may represent a substantial improvement over available therapy should involve a sufficient number of patients to be considered credible.

Breakthrough Therapy Designation

- Breakthrough therapy designation applies to the drug (either alone or in combination with other drugs) and the specific use for which it is being studied. The term drug refers to the combination of two or more drugs if the combination is the subject of the breakthrough therapy designation or request. Where appropriate, FDA may grant designation to the development of a new use of an approved drug.
- Designation as Breakthrough Therapy can be rescinded
  - Not all products designated as breakthrough therapies ultimately will be shown to have the substantial improvement over available therapies suggested by the preliminary clinical evidence at the time of designation.
  - If the designation is no longer supported by subsequent data, FDA may rescind the designation.

Breakthrough Therapy Designation Additional Information and Procedures

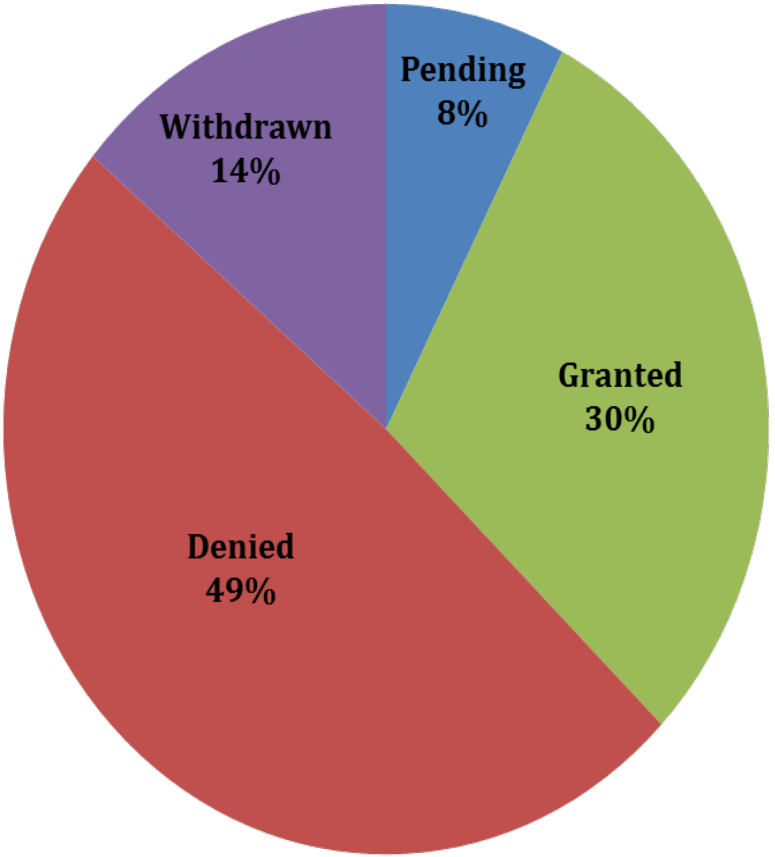
- http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm
- http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm341027.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407009.pdf

Breakthrough Therapy Designation Charts

- Center for Drug Evaluation and Research (CDER)
  - Status of Breakthrough Therapy Requests
  - Requests by CDER Division
  - Requests Granted by CDER Division
  - Total Designations Granted since Inception

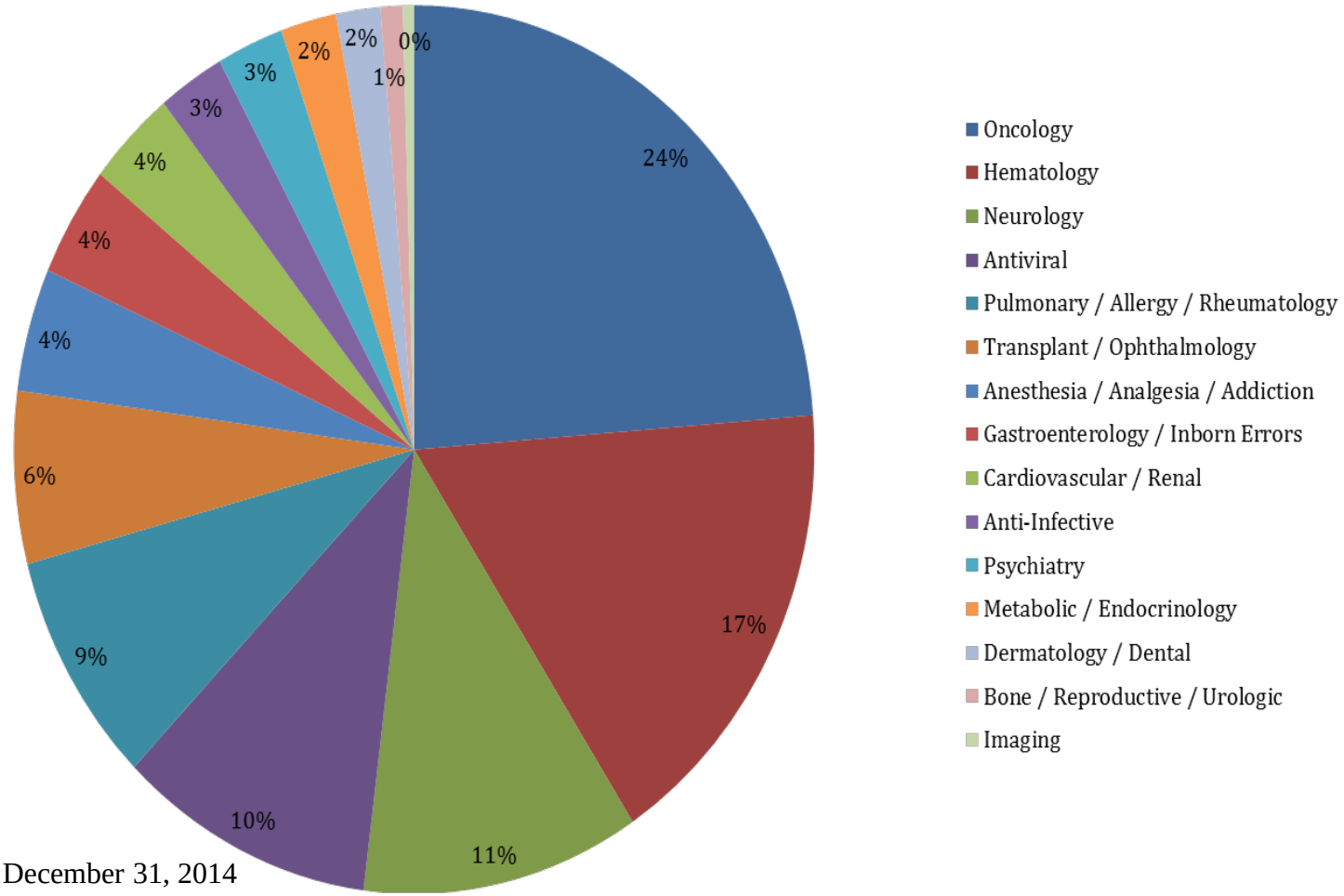
- Center for Biologics Evaluation and Research (CBER)
  - Status of Breakthrough Requests
  - Breakthrough Therapy Designations 2012-2014
  - Requests by CBER Division
  - Requests by Product Area
  - Characteristics of Requests
  - Requests Granted by CBER since Inception

Current Status of 223 CDER Breakthrough Therapy Requests



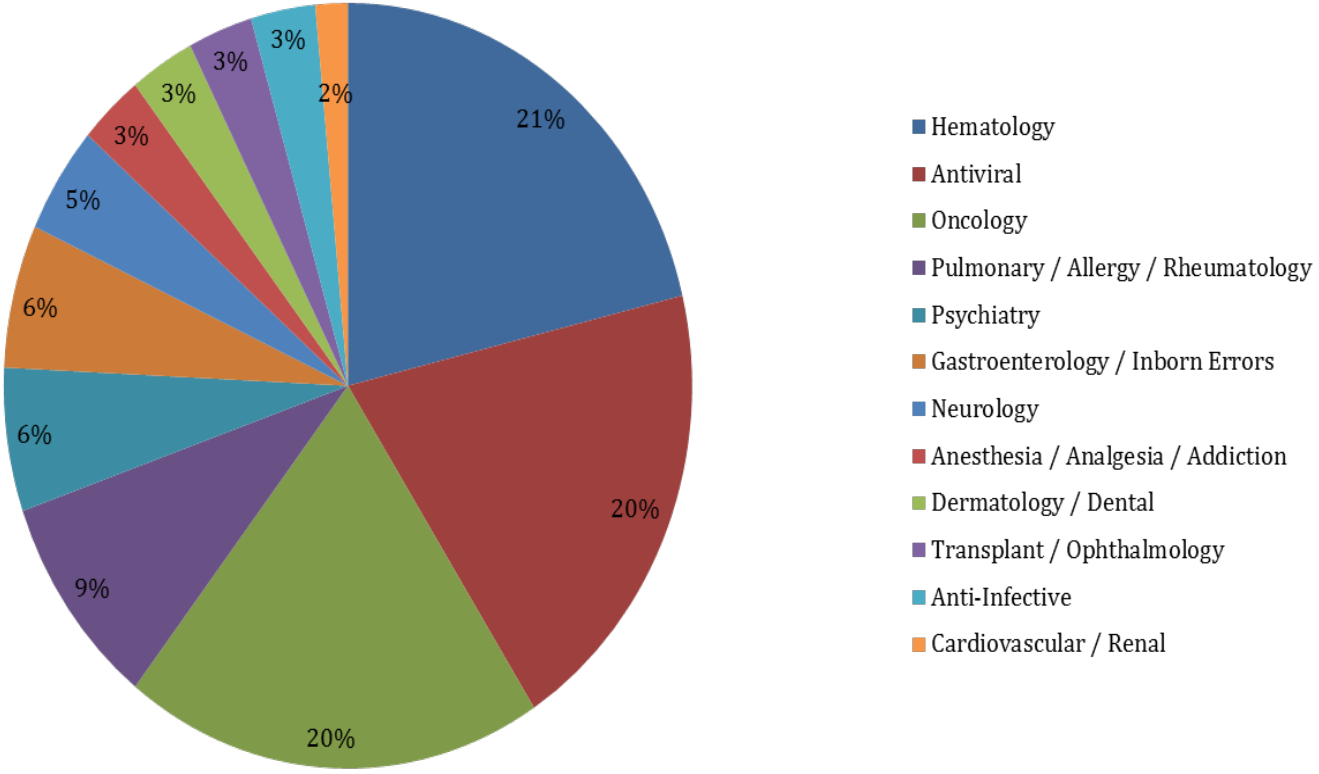
Data as of December 31, 2014

CDER Breakthrough Therapy Requests by Division



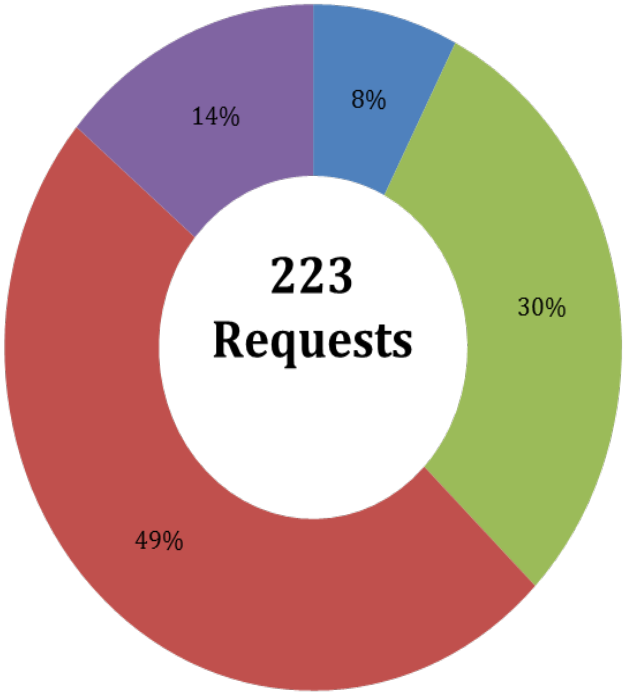
Data as of December 31, 2014

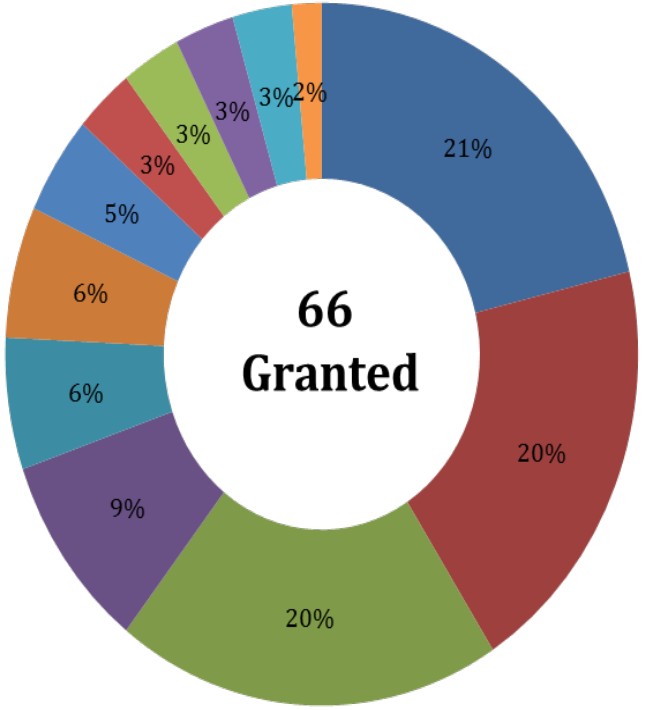
CDER Breakthrough Therapy Requests Granted by Division



Data as of December 31, 2014

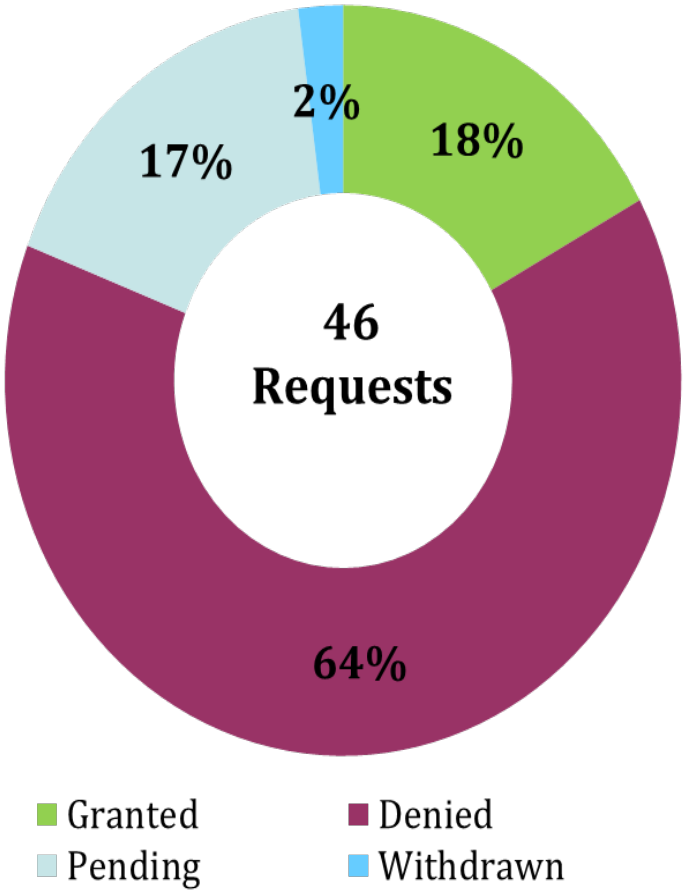
CDER has Granted 66 Breakthrough Therapy Designations since Inception





Data as of December 31, 2014

CBER Breakthrough Therapy Current Status of 46 Requests*



Data as of December 31, 2014

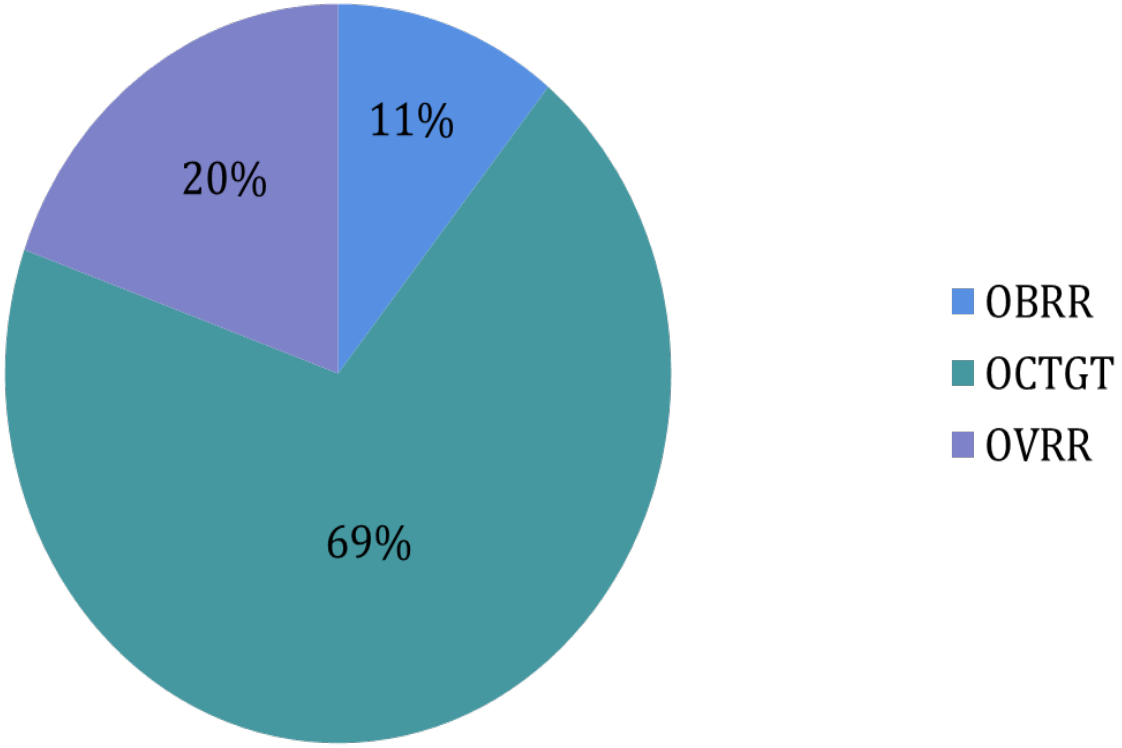
CBER Breakthrough Therapy Designations

Designations 2012 - 2014

Total Requests Received	Granted	Denied	Performance[1]
October 1, 2012 – September 30, 2013			
11	1	10	100%
October 1, 2013 – September 30, 2014			
26	7	19	92%
October 1, 2014 – December 30, 2014			
9	0	1	100%

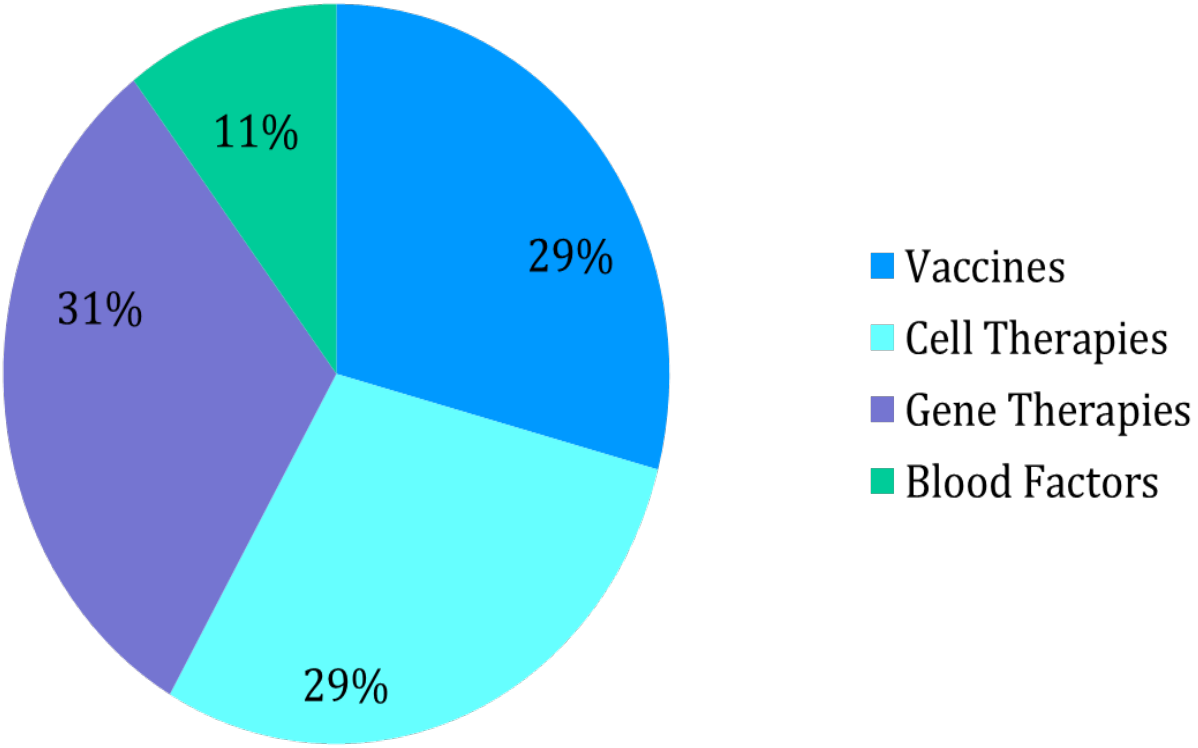
[1] Percent where action for BT designation was taken within 60 days of receipt

CBER Breakthrough Therapy Requests by Product Office*



Data as of December 31, 2014

CBER Breakthrough Therapy Requests by Product Areas*

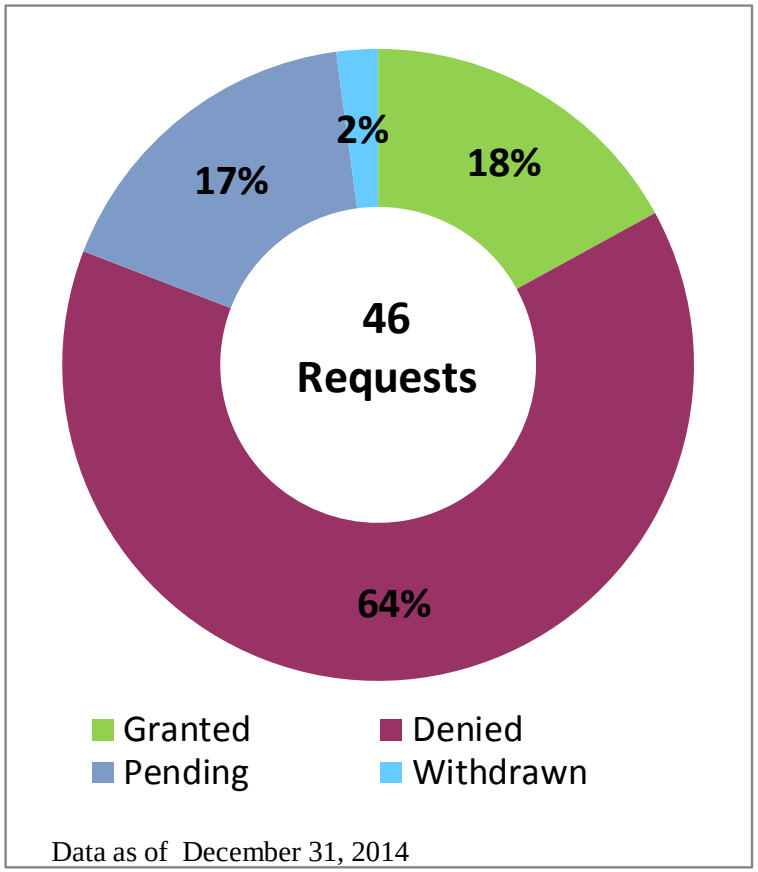


Data as of December 31, 2014

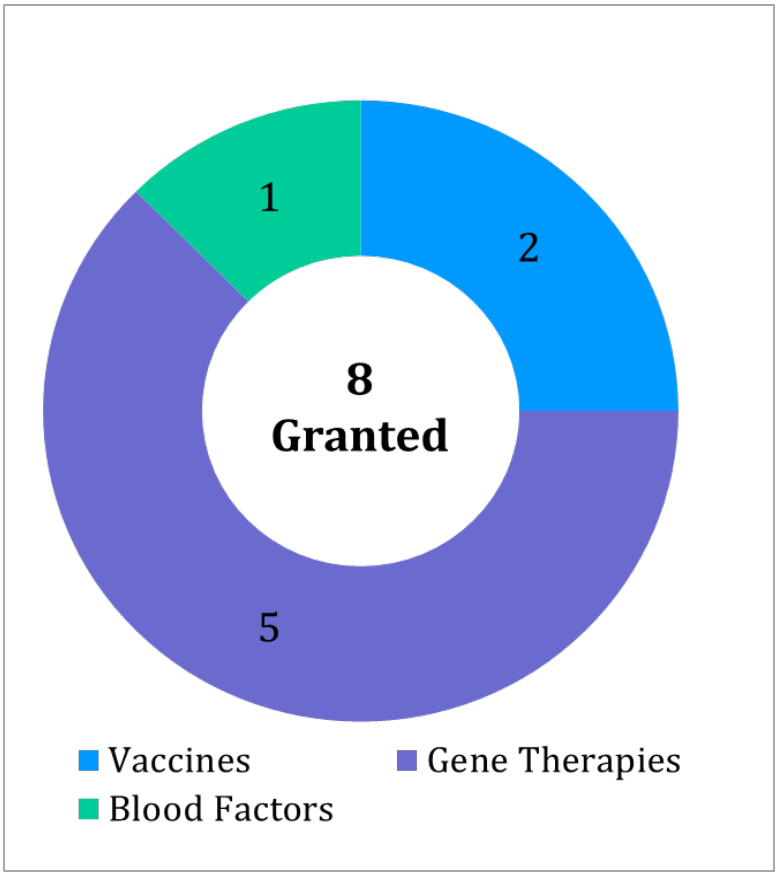
Characteristics of CBER BT Requests

- Orphan Product – 6 designations, 2 requests
- Fast Track Status – 15 granted, 3 denied
- Phase of clinical trial at time of request
  - Phase 1 – 13%
  - Phase 2 – 45%
  - Phase 3 – 41%
  - 1 in Biologics License Application (BLA)

CBER has Granted 8 Breakthrough Therapy Designations since Program Inception



Data as of December 31, 2014



Thank you

For further information or questions, please contact:

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After 27 February 2015

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