Expedited Programs and Challenges to Biologics Manufacturing

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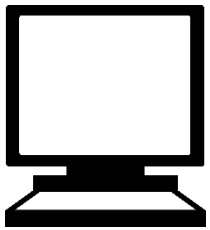
Disclaimer

- **The opinions and views expressed herein are my own and not necessarily reflective of those of the FDA or current policy**

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



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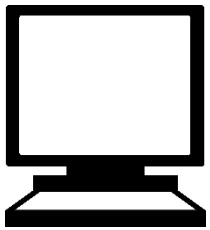



Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


FDA
It is what gives patients confidence in their *next* dose of medicine.

EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS

Expedited Programs

- Address unmet medical needs in the treatment of a serious or life-threatening condition
- Facilitate and expedite development and review of new drugs

Expedited Programs

- Fast Track Designation
- Breakthrough Therapy Designation
- Accelerated Approval
- Priority Review Designation
- Regenerative Medicine Advanced Therapy (RMAT) Designation

Fast Track Designation*

- Frequent interaction with review team
- Potential for priority review if supported by clinical data
- Rolling BLA/NDA submission

*FDASIA Title IX, Section 901 (2012); FDAMA 1997; 506(b) Food Drug and Cosmetics Act

Breakthrough Therapy Designation

- Breakthrough drug “ …preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints,…”

*FDASIA Title IX, Section 902 (2012); 506(a) Food Drug and Cosmetics Act

Breakthrough Therapy Designation

- Increased frequency of meetings/communications
- Timely advice to facilitate an efficient development program
- Senior management involvement
- Experienced review staff

Breakthrough Designation

- FDA may grant:
  - Fast Track Designation
  - Priority review
  - Expedited review
    - Action is planned for at least one month prior to PDUFA goal date, if:
      - » No unexpected review issues arise
      - » Review team does not experience unexpected shift in work priorities or staff

Accelerated Approval*

- Surrogate endpoint reasonably likely to predict clinical benefit
- Clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, reasonably likely to predict an effect
- Sponsor must agree to conduct post-marketing confirmatory trials

*FDASIA Title IX, Section 901 (2012); 506(c) Food Drug and Cosmetics Act; 21 CFR part 314 subpart H; 21 CFR 601 subpart E

Priority Review

- Drug that treats a serious condition and if approved would provide significant improvement in safety and effectiveness
- Shortens the review timeline from 12 to 8 months
- Sponsor can request priority review with original NDA/BLA
  - FDA grants priority review within 60 days of submission, assigned at time of filing.

Regenerative Medicine Therapies (RMT)

- 21st Century Cures Act Signed into law in December 2016
  - Section 3033 of the Cures Act amended section 506 of the FD&C Act
  - Addresses expedited development and review of products categorized as RMT
  - Creates pathway for designation as a regenerative medicine advanced therapy (RMAT)
    - Regenerative Advanced Therapy = Regenerative Medicine Advanced Therapy (RMAT)

Regenerative Medicine Advanced Therapy (RMAT) Designation

- An investigational drug is eligible for designation if:
  - If it meets the definition of RMT
  - The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
  - Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

RMAT Designation

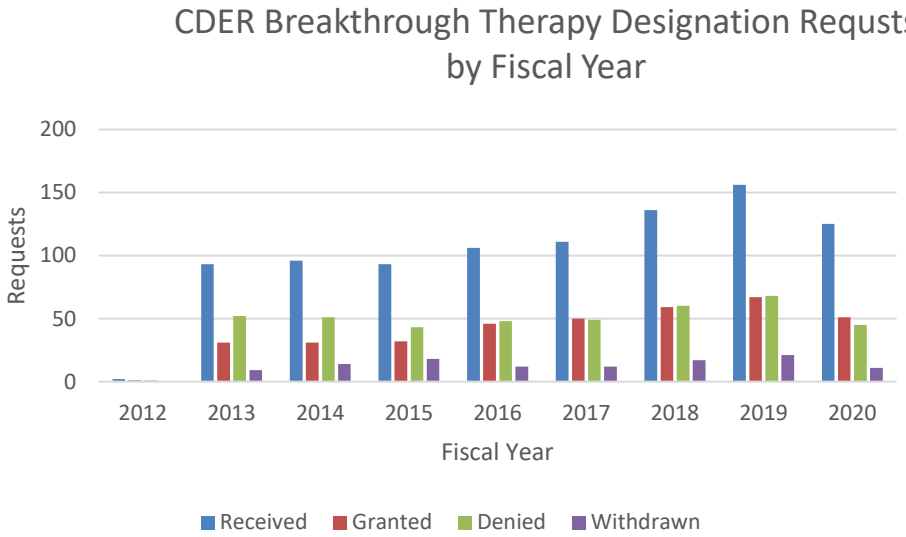
- Advantages of the RMAT designation include all of the benefits of the Fast Track and Breakthrough Designation programs
- Early interactions with FDA to discuss any potential surrogate or intermediate endpoints to support accelerated approval
- May be eligible for priority review

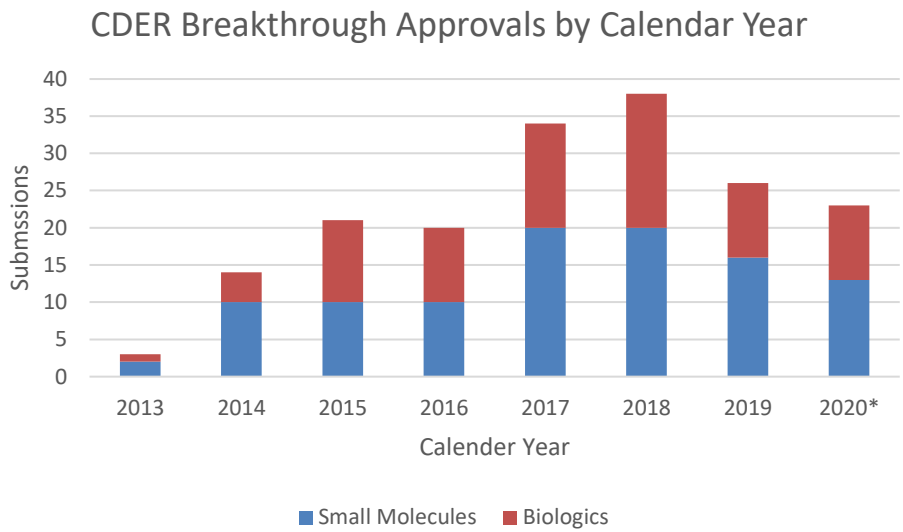
RMAT Designation

- More frequent meetings with FDA review team and management, in addition to PDUFA formal meetings (e.g., EOP2, pre-BLA), to discuss critical issues
  - Meetings are typically granted as Type B, either teleconference or face-to-face

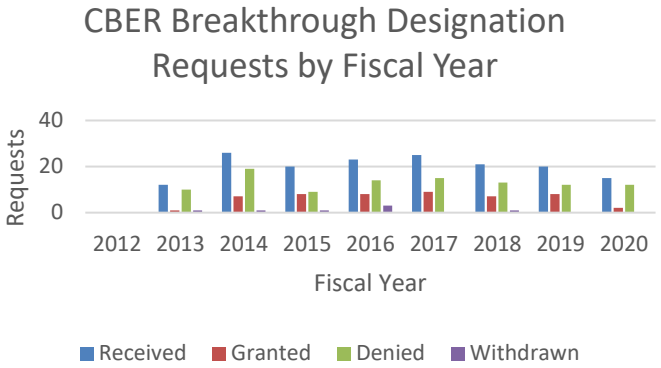
- RMAT Initial Comprehensive Multidisciplinary meeting (Type B)
  - Granted as a Type B meeting, typically face-to-face
  - Can be a standalone meeting, or combined with an IND milestone meeting (e.g., EOP2, pre-BLA)
  - Purpose of the meeting is to understand the product development program and facilitate communication between sponsor and FDA

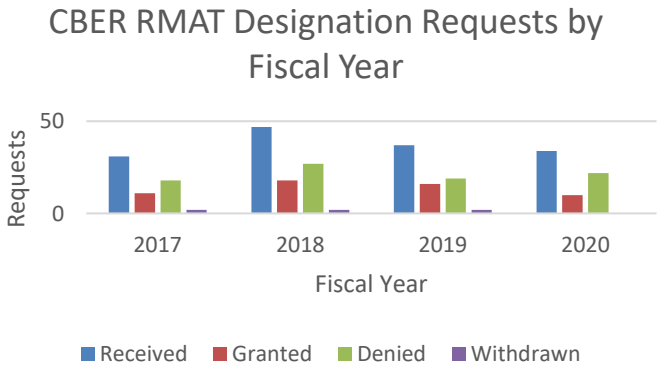
CDER Breakthrough Therapy Requests and Approvals

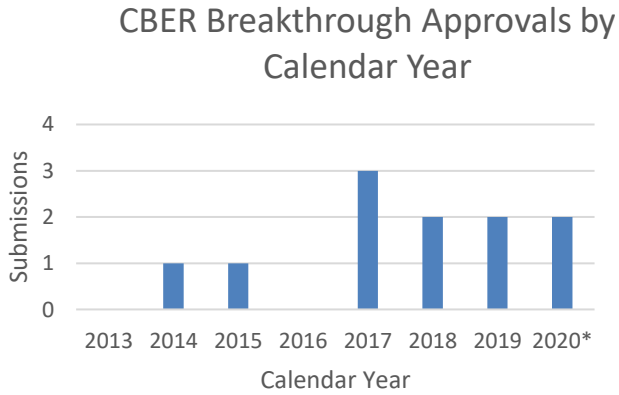




CBER Breakthrough and RMAT Requests and Approvals

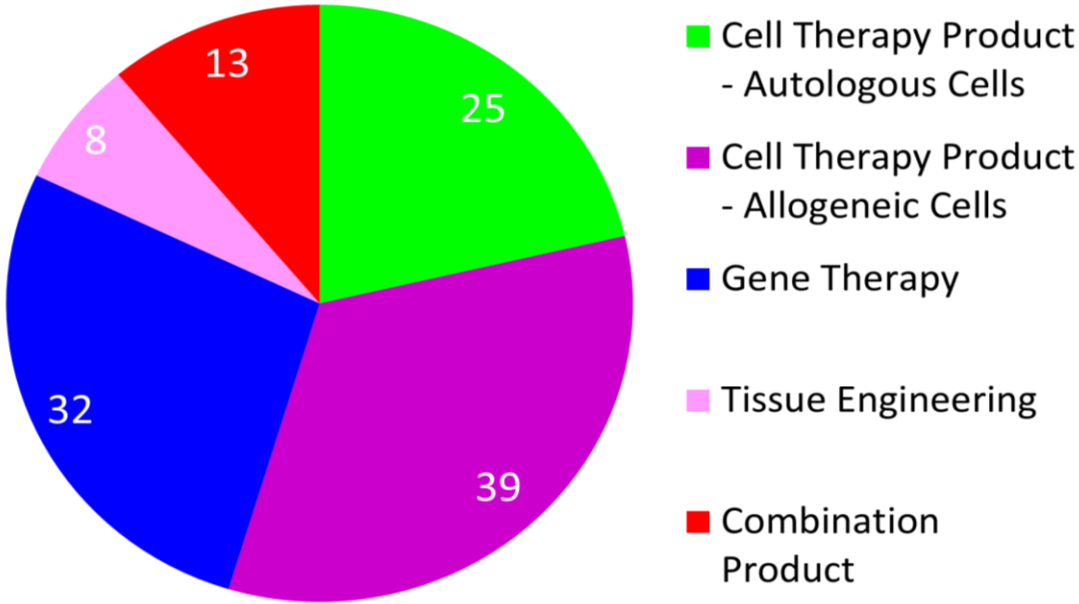






RMAT Designation Requests as of August 16, 2019

Distribution by Product Type



Expectations for Quality

Patients and caregivers assume that their drugs:

- Are safe
- Are efficacious
- Have the correct identity
- Deliver the same performance as described in the label
- Perform consistently over their shelf life
- Are made in a manner that ensures quality
- Will be available when needed

Challenges for Breakthrough Therapy Manufacturing

- Alignment of CMC development timelines with clinical development
  - Manufacturing changes
    - Scale
    - Clinical vs commercial process
    - Coordination with contract manufacturers
    - Container closure systems

Challenges for Breakthrough Therapy Manufacturing

- Comparability Studies
  - Planned and executed under compressed timelines
- Process Qualification
  - Planned and executed under compressed timelines
- Setting specifications with few lots

Product Quality and Manufacturing

- Early
  - Understanding mechanism of action
  - Identification of critical quality attributes
  - Identification of the container closure system and formulation

Product Quality and Manufacturing

- Early
  - Planning for manufacturing changes – minimize need for comparability studies
  - Development of reference materials
  - Validation of critical assays

Product Quality and Manufacturing

- To streamline process development and qualification
  - Leverage:
    - Prior knowledge
    - Design of experiment study results
    - Modeling

Product Quality and Manufacturing

- Streamline Process Qualification
  - May be able to perform some activities in parallel
    - E.g. some DP PV runs may use DS made using non-PV
  - Comparability protocols
  - Concurrent validation approaches
  - Post-approval life-cycle management plans

Specifications

- Leverage:
  - The target product profile
  - Mechanism of action
  - Critical quality attribute understanding
  - Real time and forced degradation stability dats
  - Platform knowledge

Conclusions

- CDER and CBER expedited programs:
  - Fast Track Designation
  - Breakthrough Designation
  - Accelerated Approval
  - Priority Review Designation
  - Regenerative Medicine Advanced Therapy (RMAT) Designation
- There has been rapid uptake of breakthrough designation since 2012
  - ~190 breakthrough approvals
  - ~1229 breakthrough designation requests
  - ~437 breakthrough designations granted

Conclusions

- The rapid development of breakthrough therapies presents product quality and manufacturing challenges
- Good and early planning facilitates rapid manufacturing development
- Leveraging prior knowledge, DOE studies, and modelling may streamline manufacturing process development and qualification
- Understanding of mechanism of action, critical quality attributes, and product stability facilitates manufacturing development, specification setting, and establishing dating periods

Many, many, thanks…

- Miranda J Raggio
- Chikako Torigoe
- Leslie Rivera-Rosado

BTD Program Resources

- MAPP 6025.6: Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

- MAPP 6025.7: Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM437281.pdf

- Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics:

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

BTD Program Resources-2

- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

https://www.fda.gov/media/120267/download

- MAPP 6030.9: Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review

http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm349907.pdf

- BT Information on fda.gov:

http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm329491.htm

- Section 902 of FDASIA:

http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf

Thank you for your time

Have a great conference!!!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