FDA Expedited Programs and Regenerative Medicine Advanced Therapy Designation

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Learning Objectives

- List the FDA Expedited Programs
- Understand the criteria for FDA Expedited Programs
- Describe the Regenerative Medicine Advanced Therapy Program

Outline

- FDA's Expedited Programs
- Regenerative Medicine Advanced Therapy Designation (RMAT)
- FDA's Experience with RMAT

Overview of FDA Expedited Programs

- **Accelerated Approval Regulations: 1992**
  Section 506(c) of Food, Drug & Cosmetic Act (FD&C Act)
- **Priority Review Designation: 1992**
  Prescription Drug User Fee Act
- **Fast Track Designation (FTD): 1997**
  Section 506(b) of FD&C Act, as added by section 112 of the Food and Drug Administration Modernization Act
- **Breakthrough Therapy Designation (BTD): 2012**
  Section 506(a) of the FD&C Act, as added by section 902 of the Food and Drug Administration Safety and Innovation Act
- **Regenerative Medicine Advanced Therapy (RMAT): 2016**
  Section 506(g) of the FD&C Act, as added by section 3033 of the 21st Century Cures Act

Comparison of Expedited Programs Criteria

Accelerated Approval	Priority Review	Fast Track	Breakthrough Therapy [1]	RMAT [2]
Serious condition AND Meaningful advantage over available therapies Demonstrates an **effect on** either: a **surrogate endpoint** or intermediate clinical endpoint	**Serious condition** AND Demonstrates potential to be a significant **improvement in safety or effectiveness**	**Serious condition** AND Nonclinical or clinical data demonstrate the *potential* to address unmet medical need	**Serious condition** AND Preliminary clinical evidence indicates that the drug may demonstrate **substantial improvement over available therapy** on one or more clinically significant endpoints	**Serious condition** AND a regenerative medicine therapy AND Preliminary clinical evidence indicates that the drug has the **potential to address unmet medical needs** for such disease or condition

[1] FDA Guidance for Industry: Expedited Programs for Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
[2] FDA Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, February 2019

Comparison of Expedited Programs Features

Accelerated Approval	Priority Review	Fast Track (FT)	Breakthrough Therapy (BT) [1]	RMAT [2]
Approval based on surrogate or intermediate clinical endpoints **Save valuable time** in the drug approval process **Reduce waiting period for patients to obtain clinically meaningful benefit.** **Confirmatory trials to verify and describe the clinical benefit**	**Shortened Review** Clock FDA will take action on an application within 6 months (compared to 10 months under traditional review)	**Frequent meetings** **Eligibility** for *: ✓ Priority Review ✓ Rolling Review *if relevant criteria are met	**All FT Features, including:** Actions to expedite development and review; Rolling review **+** **Intensive** guidance on an efficient drug development program **Organizational** commitment involving senior managers	**All FT and BT Features,** **including** early interactions to discuss any potential surrogate or intermediate endpoints **+** **Statute** addresses potential ways to support accelerated approval

[1] FDA Guidance for Industry: Expedited Programs for Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014
[2] FDA Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions, February 2019

Challenge Question 1

Which one of the following is not an FDA Expedited Program?

a. RMAT
b. Fast Track Designation
c. Traditional Approval
d. Priority Review

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d. Priority Review

RMAT Designation Program

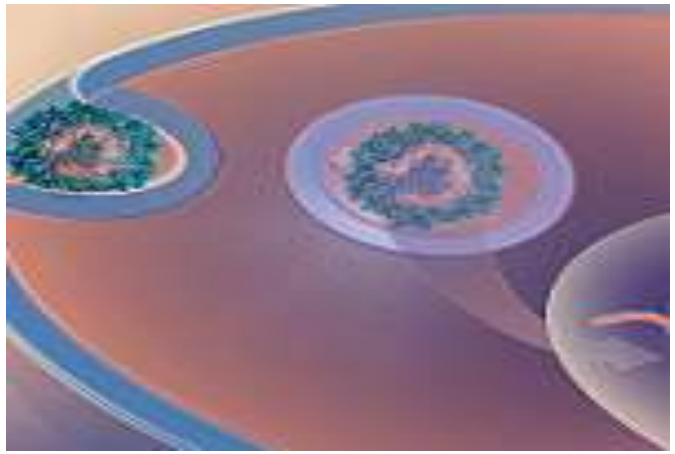
Regenerative Medicine Advanced Therapy (RMAT)

- **21st Century Cures Act: Title III, Section 3033**
  - Signed into law in 2016
  - Creates pathway for designation as a regenerative medicine advanced therapy
- **Definition of Regenerative Medicine Therapy:**
  - Cell therapy, therapeutic tissue engineering products, human cell and tissue products, or any combination product using such therapies or products
  - Combination product can be eligible for RMAT designation when the biological component provides the greatest contribution to the overall intended effects of the combination product
  - FDA interpretation of Section 3033 of the 21st Century Cures Act adds: “Gene therapies, including genetically modified cells, that lead to a sustained effect on cells or tissues”

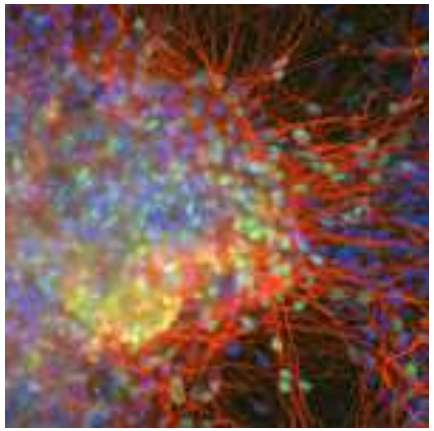
Regenerative Medicine Advanced Therapy (RMAT) Designation Criteria

- **An investigational drug meets the definition of regenerative medicine therapy**
- **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**

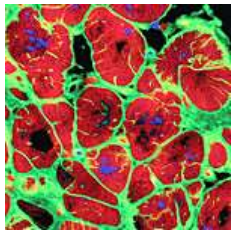
Regenerative Medicine Therapies



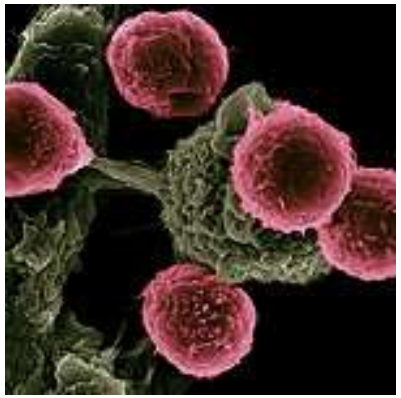
Gene therapy to treat inherited genetic disorder
Courtesy of NIH Image Gallery



iPSCs regenerated neurons
Courtesy of NIH Image Gallery



IPSCs regenerated muscle cells
Courtesy of NIH Image Gallery



Cellular therapy
Courtesy of NIH Image Gallery

Stem cells engineered to grow cartilage
Courtesy of NIH Image Gallery

Regenerative Medicine Advanced Therapy (RMAT) Designation Features

- **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**
- **Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements**

Accelerated Approval & Confirmatory Evidence

- **Under the Cures Act, RMAT-designated products may be eligible for accelerated approval based on**
  - **previously agreed-upon surrogate or intermediate endpoints that are reasonably likely to predict long-term clinical benefit; or**
  - **data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate.**

- **Sponsors of RMAT products that receive accelerated approval may be able to fulfill their postapproval requirements with clinical evidence obtained from sources other than traditional confirmatory trials. This could include:**
  - **Submission of clinical evidence, clinical studies, patient registries or other sources of real-world evidence, such as electronic health records;**
  - **Collection of larger confirmatory data sets as agreed upon during product development; or**
  - **Postapproval monitoring of all patients treated with such therapy prior to its approval**

Regenerative Medicine Advanced Therapy (RMAT) Designation Request

- **The request for RMAT designation must be made either concurrently with submission of an Investigational New Drug application (IND) or as an amendment to an existing IND**

- **FDA will notify the sponsor as to whether the regenerative medicine therapy has received the RMAT designation, no later than 60 calendar days after receipt of the designation request**

Challenge Question 2

An RMAT designation request can be submitted prior to an initial IND submission to FDA. True or false.

a. True

b. False

Challenge Question 2

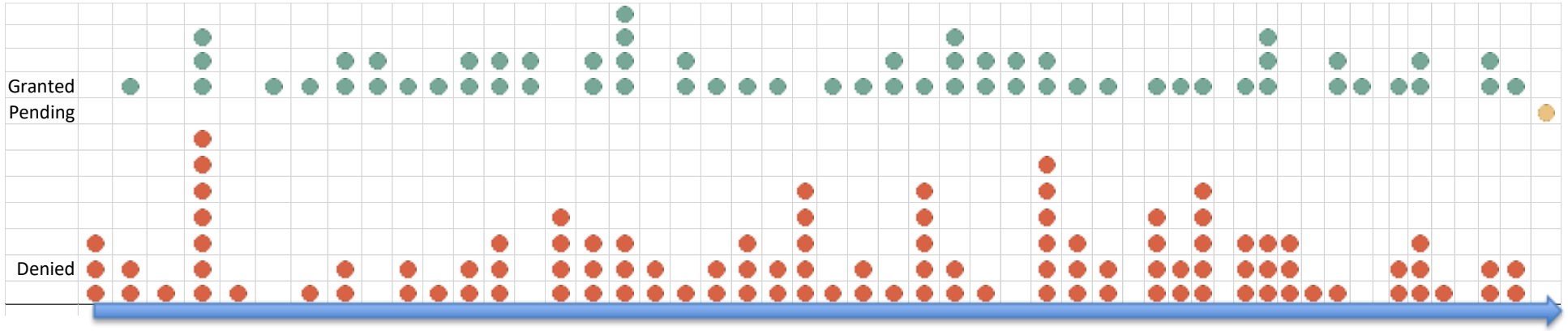
An RMAT designation request can be submitted prior to an initial IND submission to FDA. True or false.

a. True

b. False

OTAT Experience: RMAT

RMAT Designation Requests Status



12/13/2016 – 04/26/2021

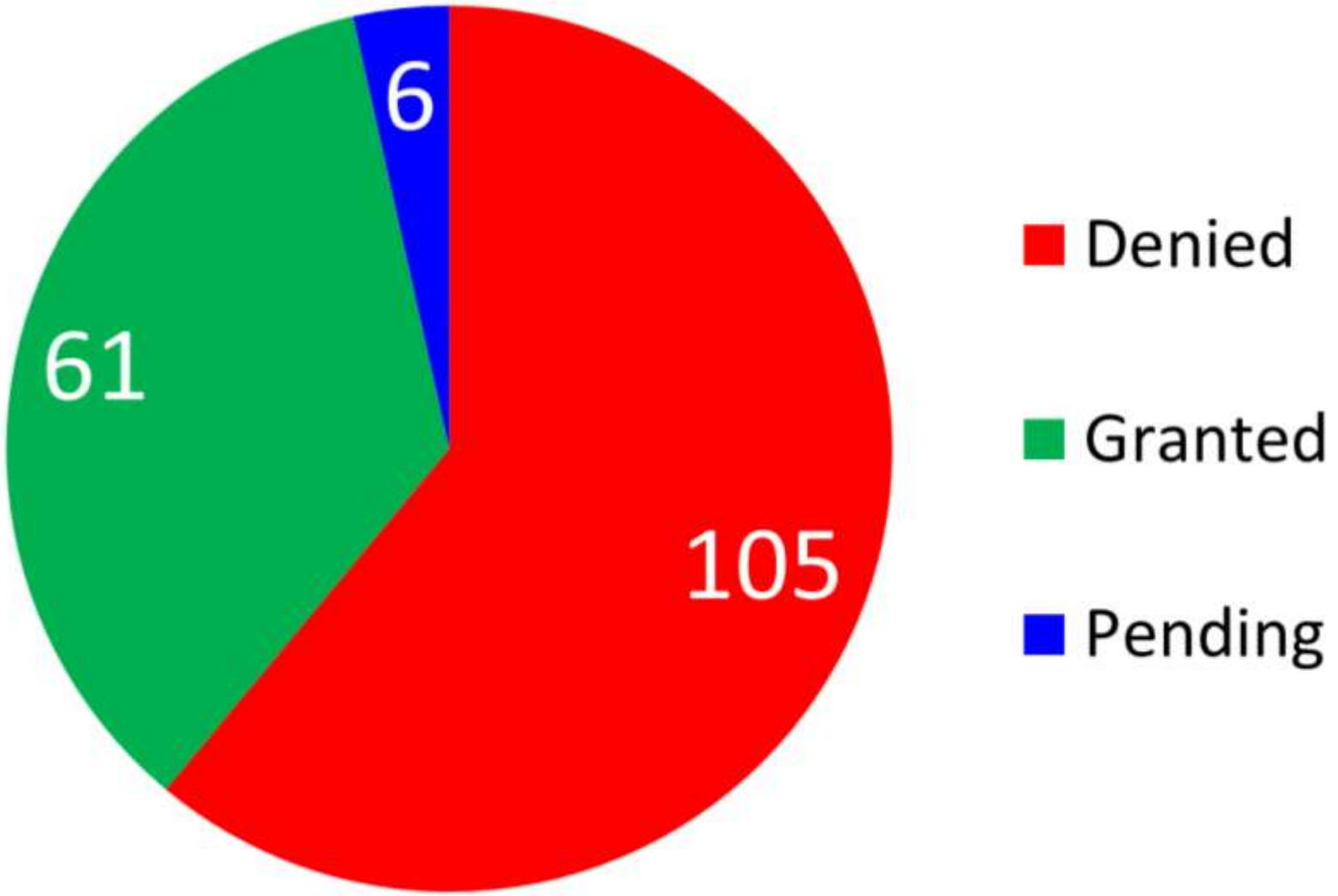
Regenerative Medicine Advanced Therapy Designation

- Up through April 26, 2021, Office of Tissues and Advanced Therapies (OTAT) has received 172 Regenerative Medicine Advanced Therapy (RMAT) Designation requests (excludes 7 withdrawn RMAT requests). Of these, 61 were granted, 105 were denied and 6 were pending.

- Of the 172 RMAT requests, 67 (40.0%) are gene therapies, 48 (27.9%) are allogeneic cell therapies, and 33 (19.2%) are autologous cell therapies.

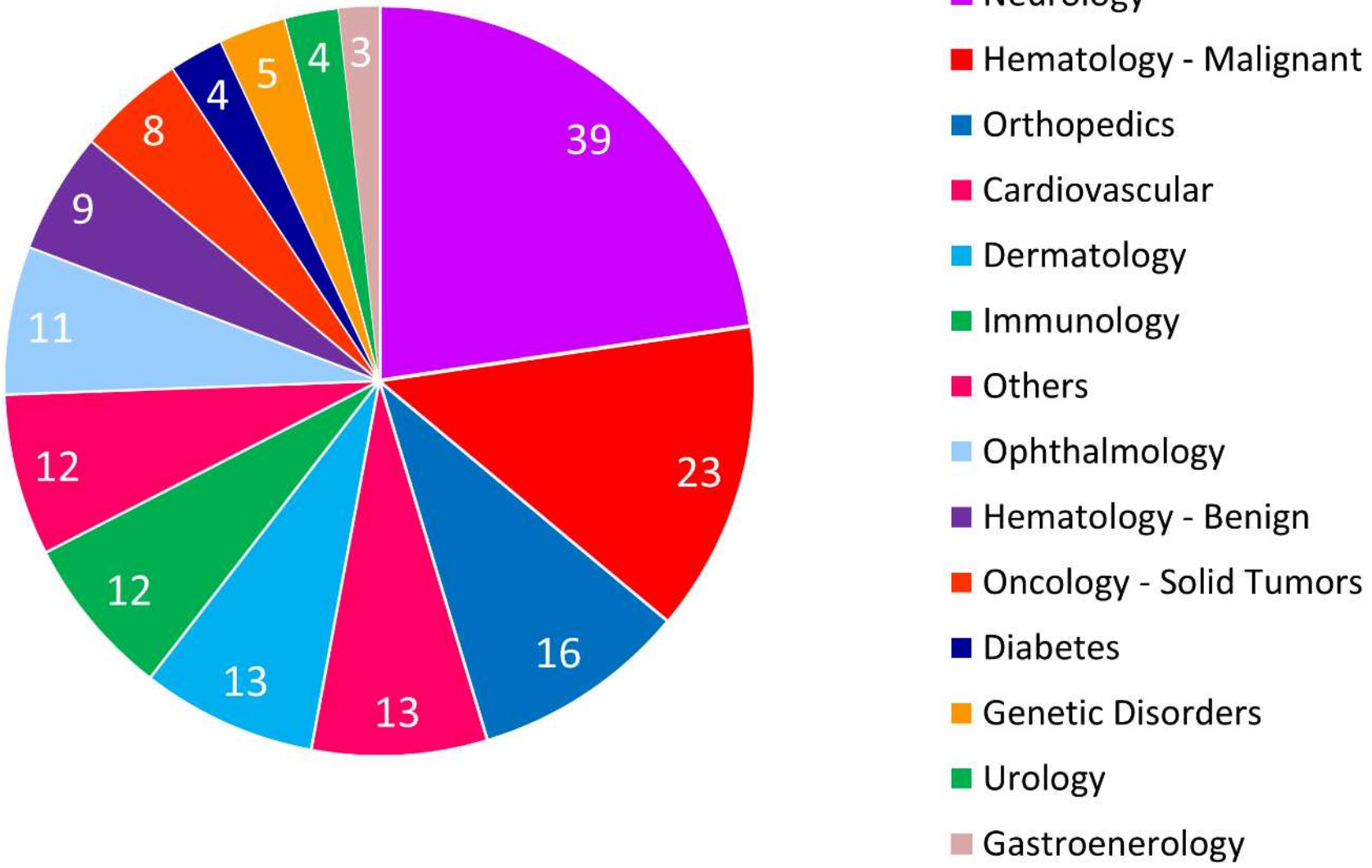
- Of the 61 granted RMAT requests, 31 (50.8%) are gene therapies, 21 (34.4%) are allogeneic cell therapies, and 4 (6.6%) are autologous cell therapies.

RMAT Designation Requests Status*

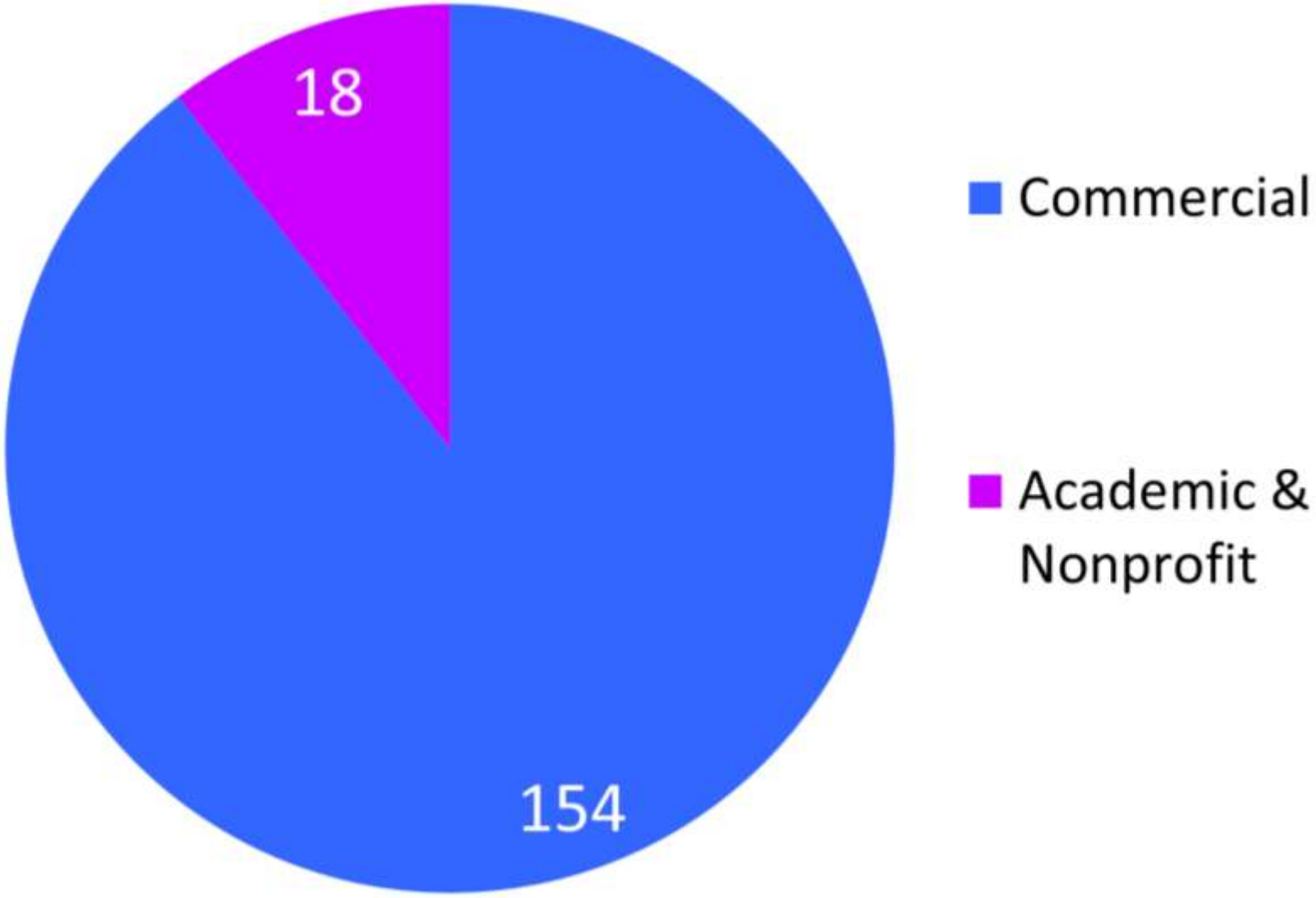


*As of April 26, 2021

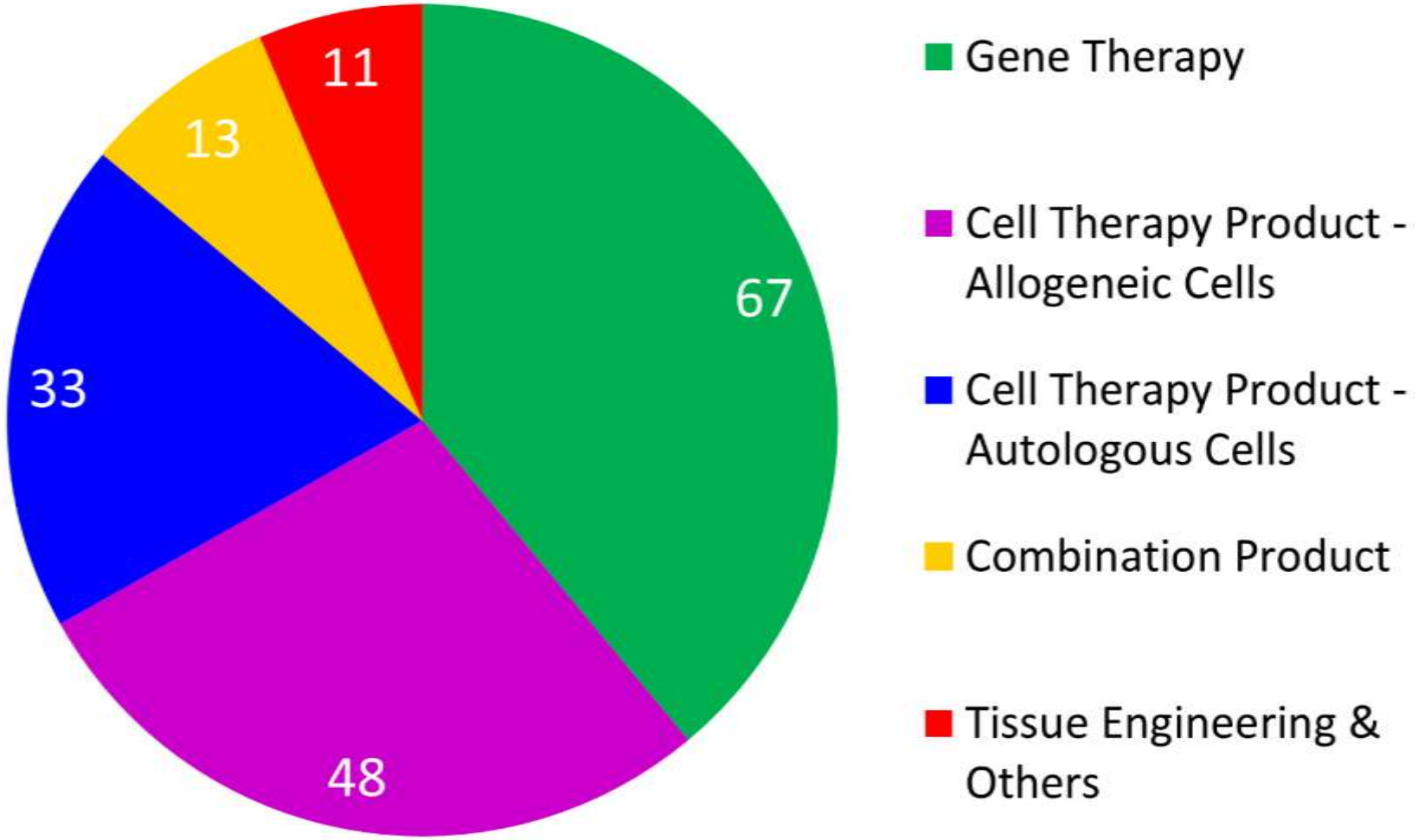
RMAT Designation Requests - Distribution by Specialty



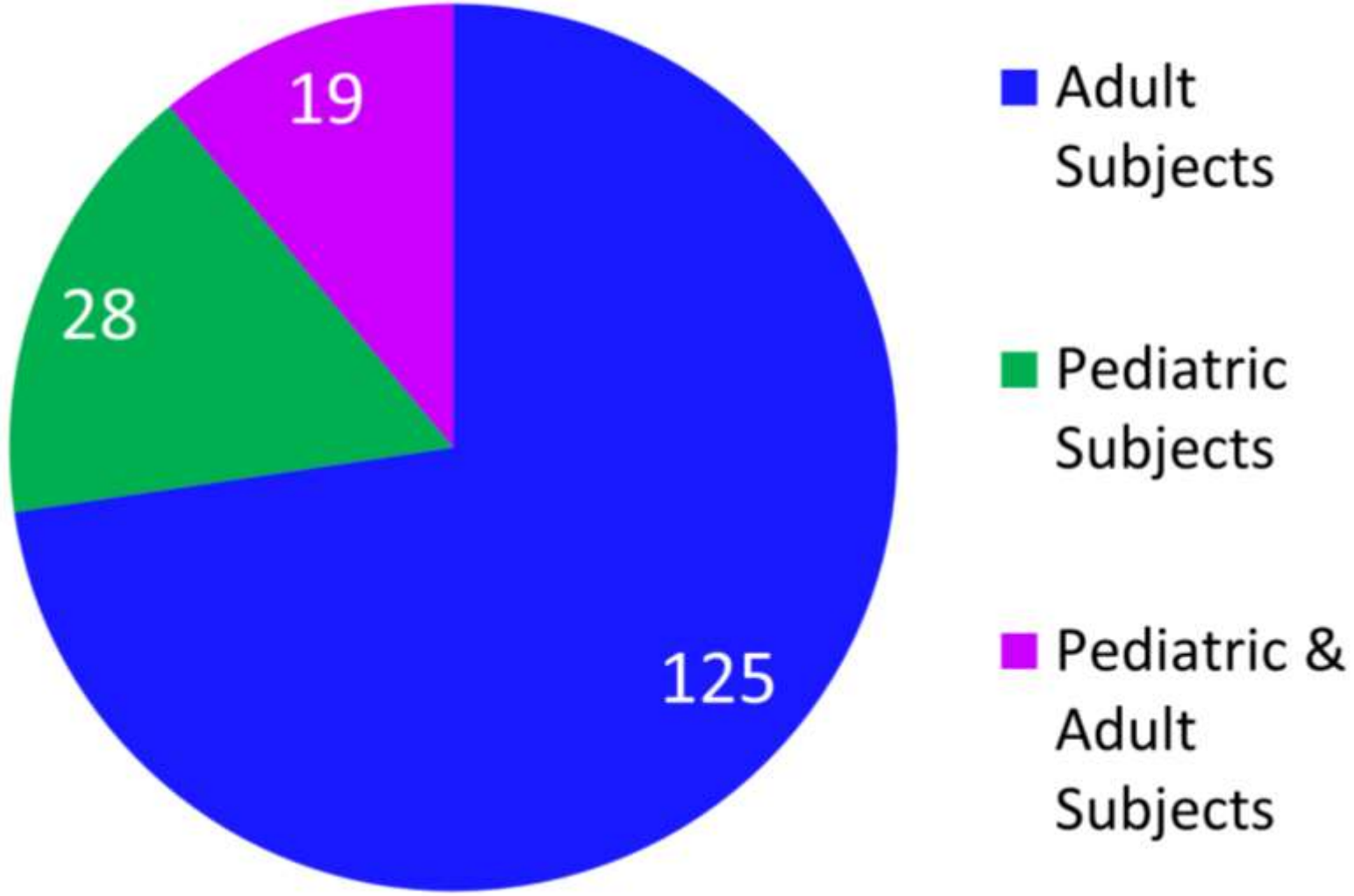
RMAT Designation Requests - Distribution by Applicant



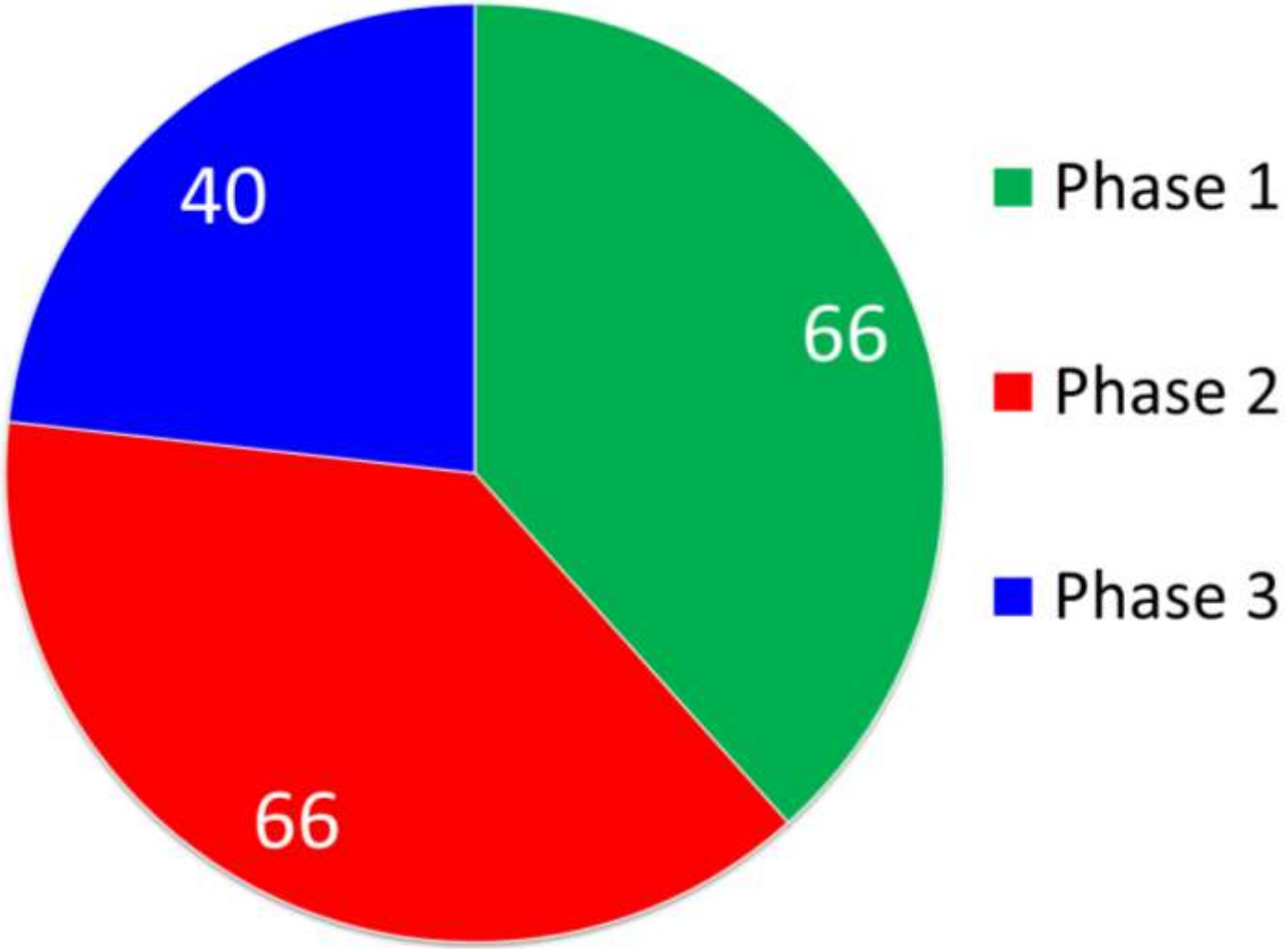
RMAT Designation Requests - Distribution by Product Type



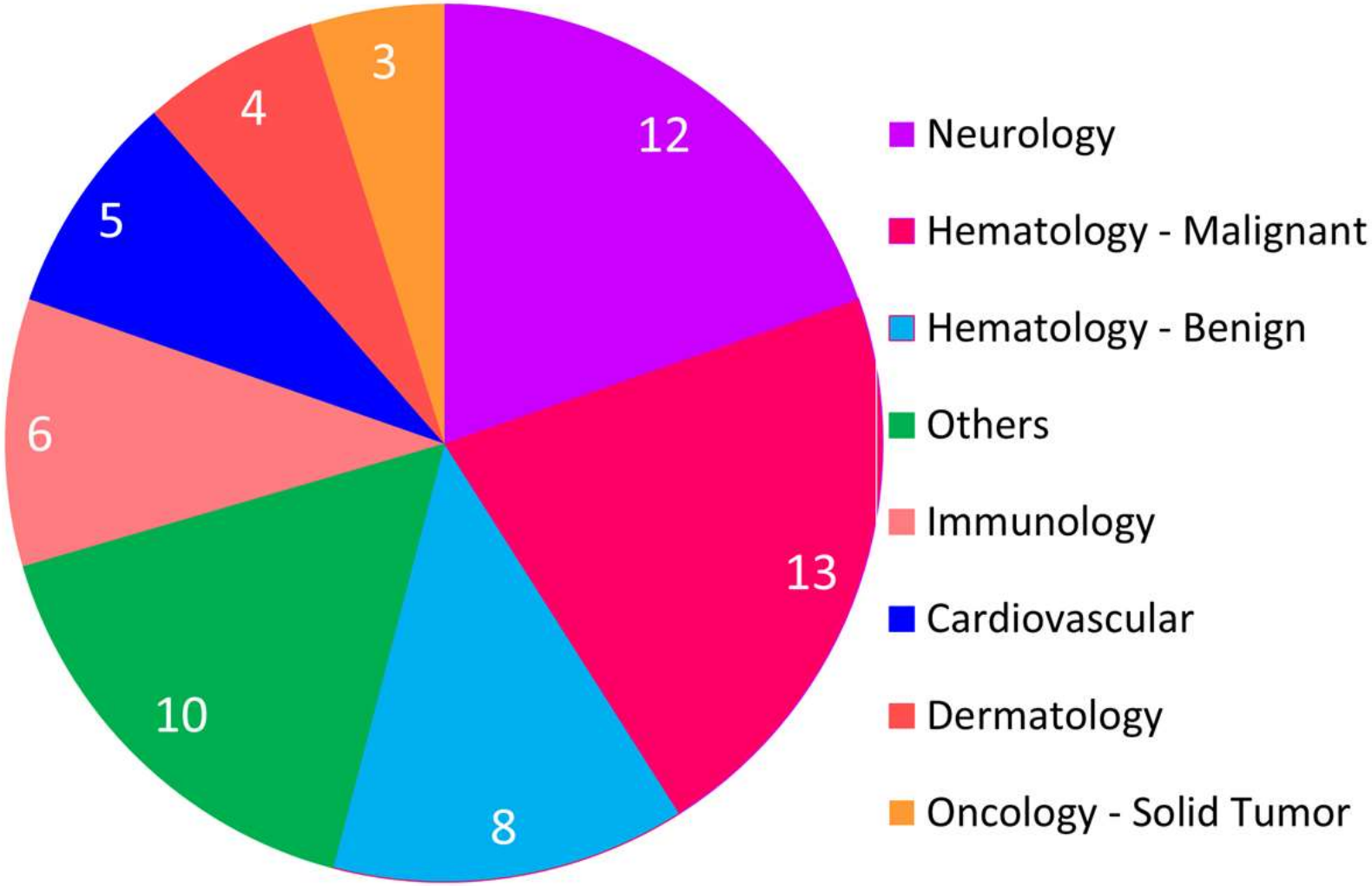
RMAT Designation Requests - Distribution by Study Population



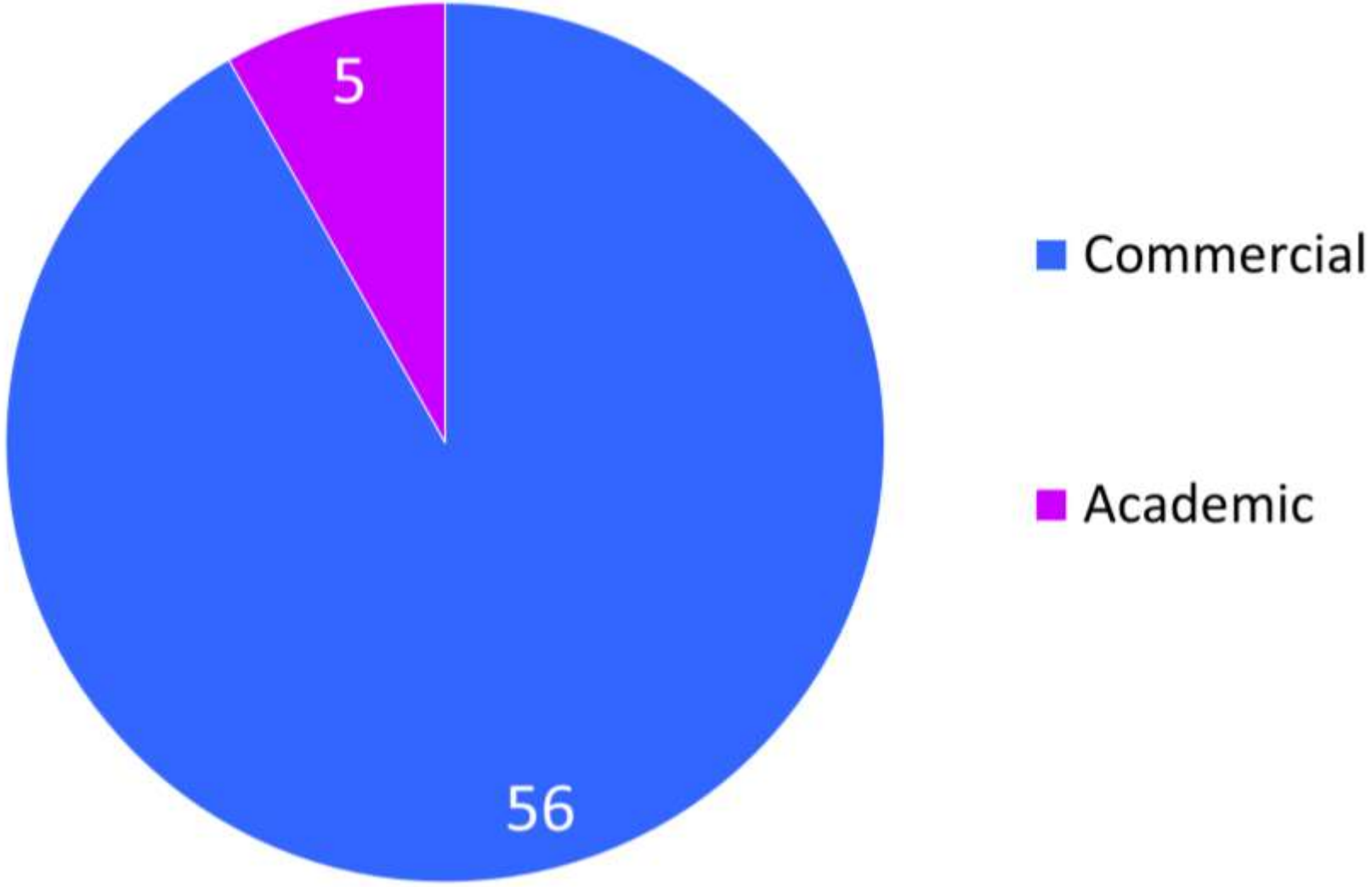
RMAT Designation Requests - Distribution by Clinical Study Status



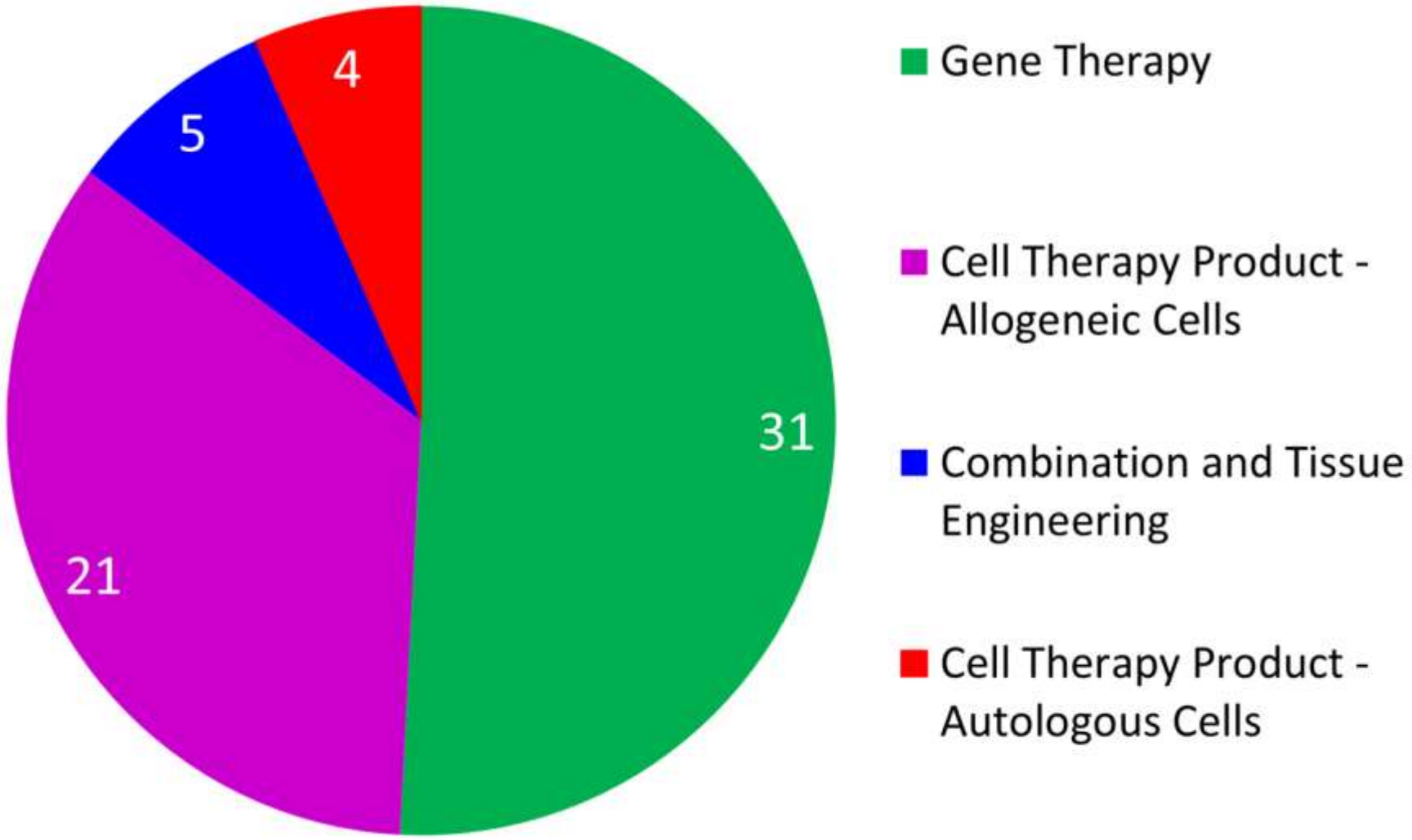
Granted: RMAT Designation Requests by Specialties



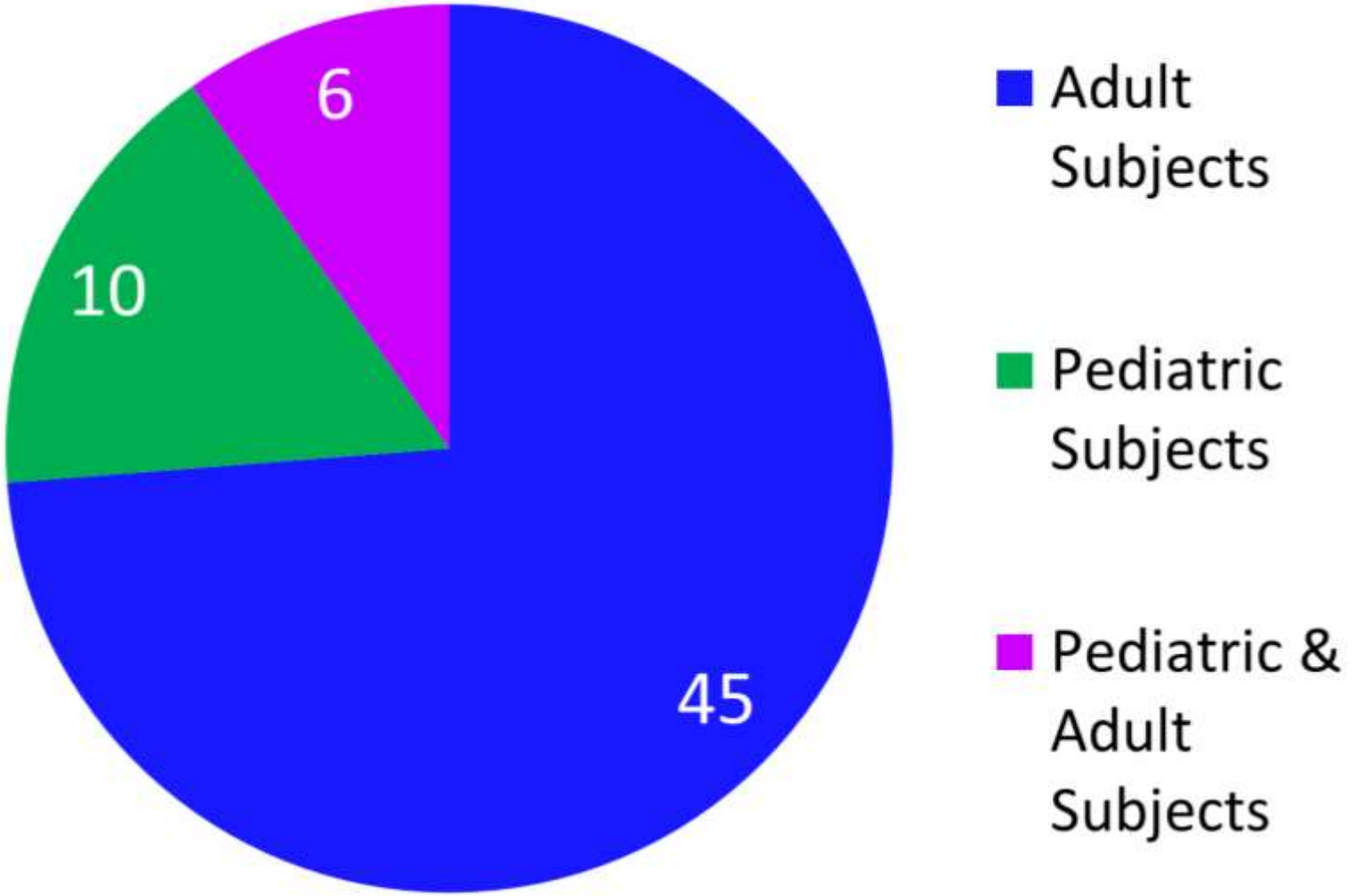
Granted RMAT Designation Requests - Distribution by Applicant



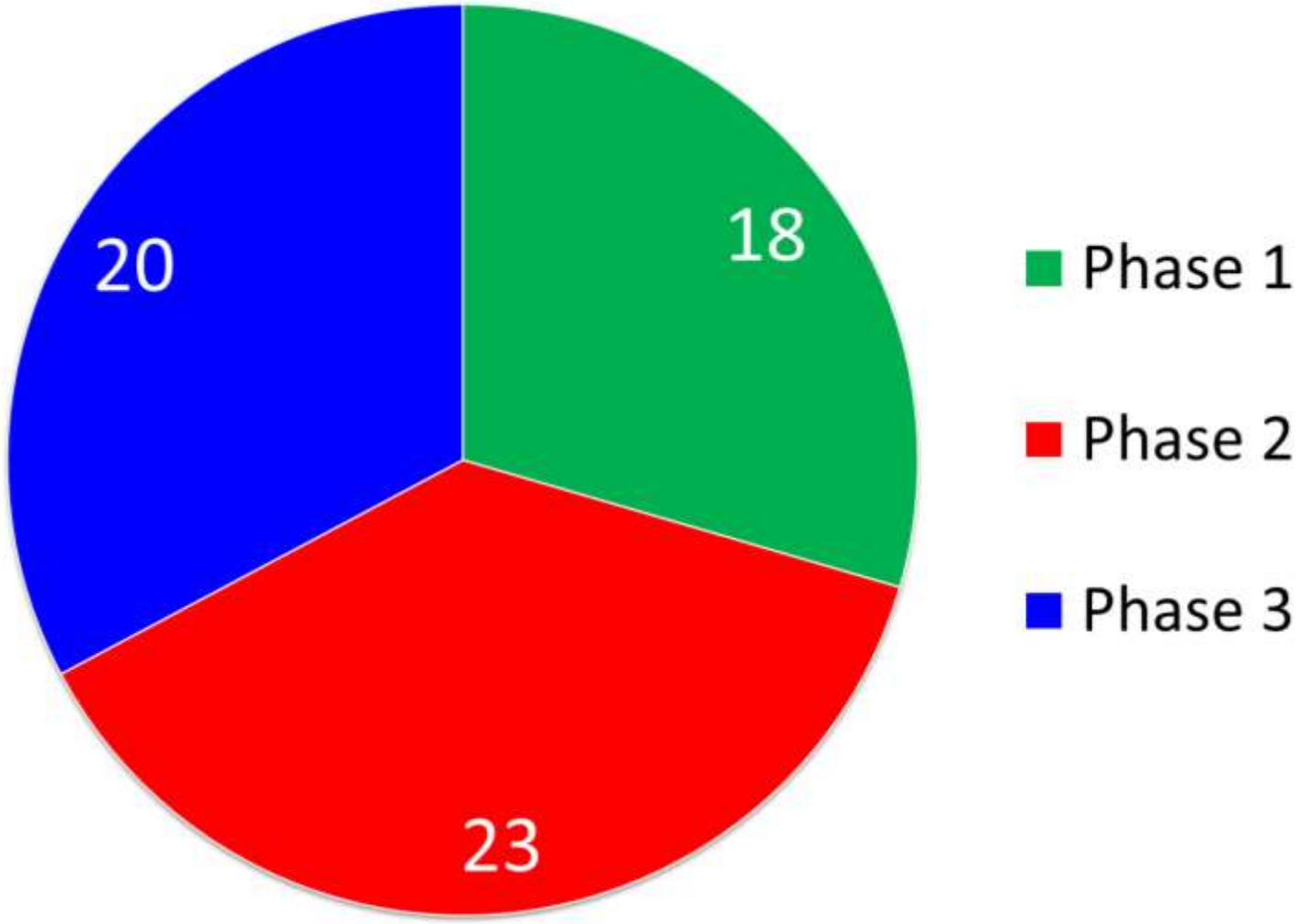
Granted RMAT Designation Requests - Distribution by Product Type



Granted RMAT Designation Requests - Distribution by Study Population



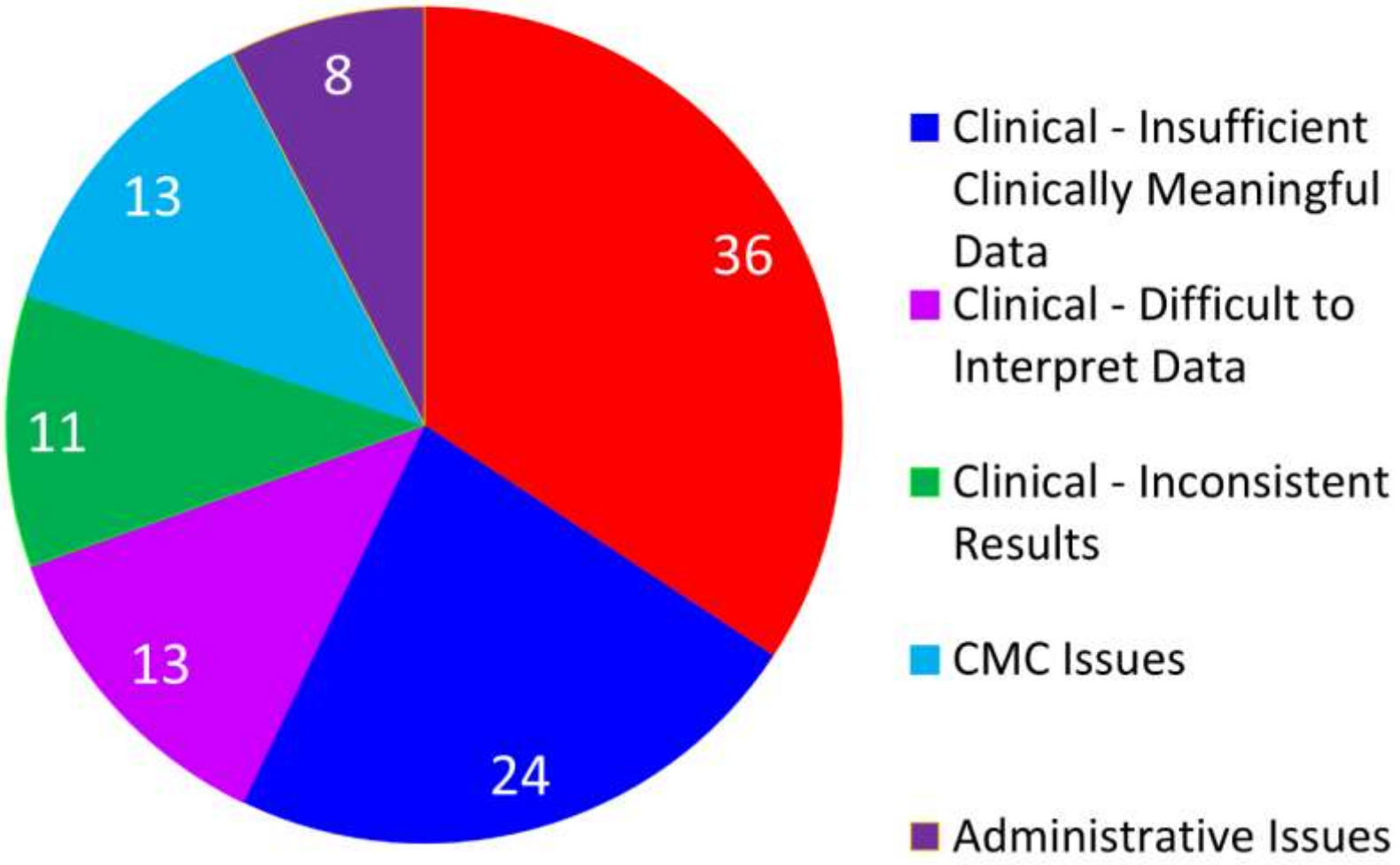
Granted RMAT Designation Requests - Distribution by Clinical Study Status



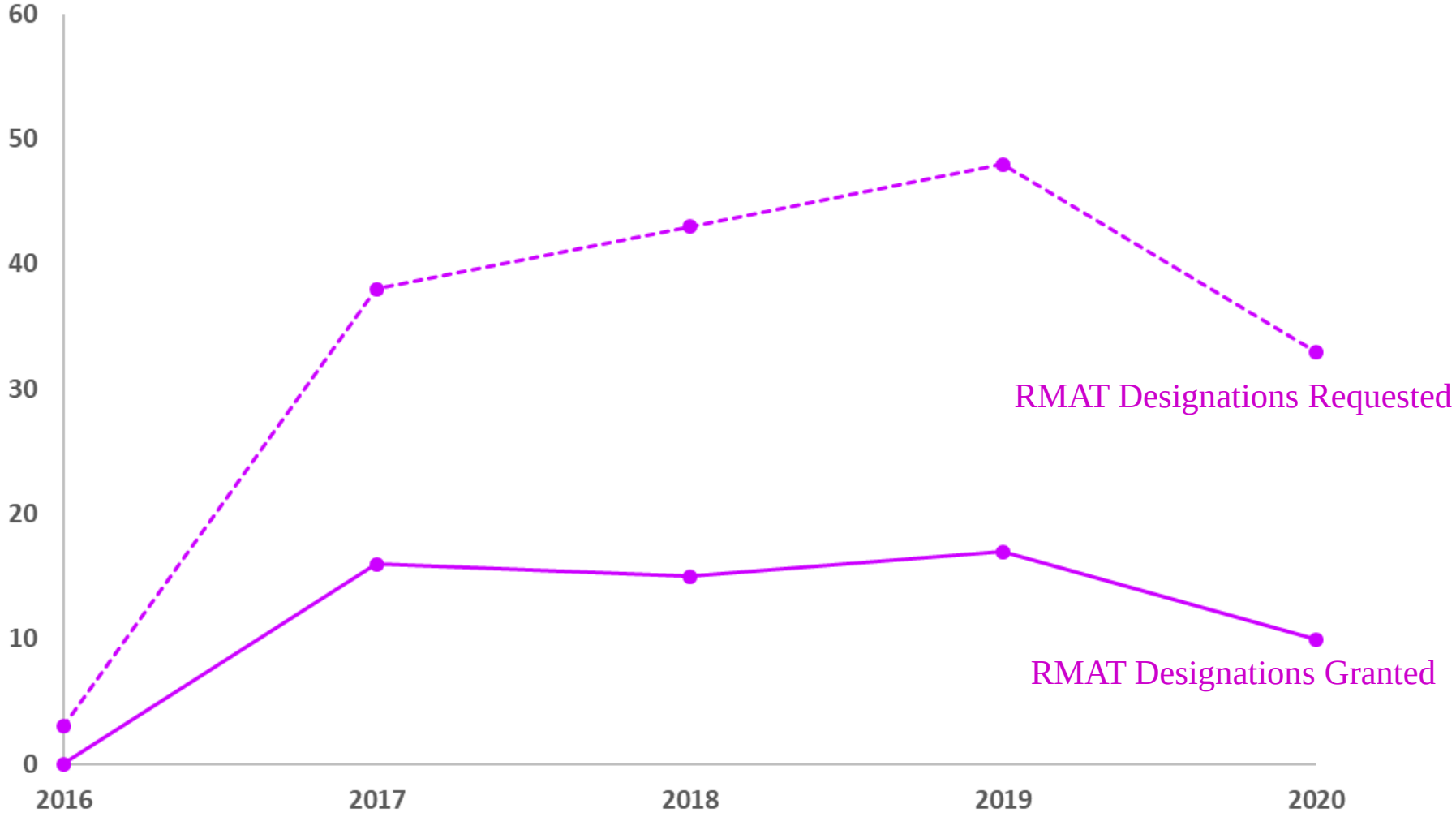
Analysis of Denied Regenerative Medicine Advanced Therapy Designation Requests

- Administrative Reasons
  - –Inactive IND
  - –No preliminary clinical evidence submitted
- CMC Reasons
  - –Different product, lack of product comparability data
  - –Not a regenerative advanced medicine therapy
- Insufficient Preliminary Clinical Evidence
  - –Study design issues
  - –Difficult to interpret data
  - –Inconsistent results among endpoints or subject subgroups
  - –Insufficient clinically meaningful data

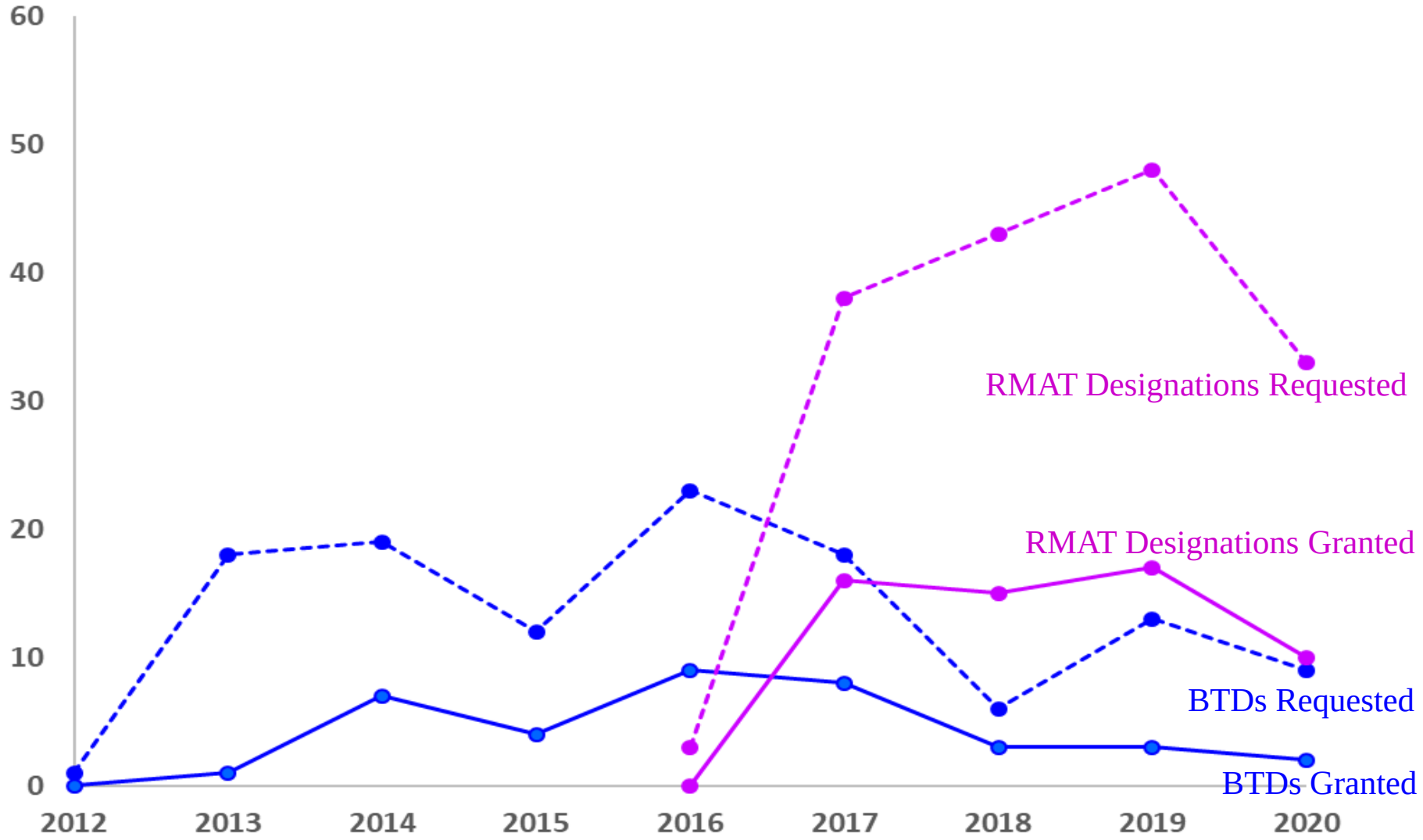
Analysis of Denied Regenerative Medicine Advanced Therapy Designation Requests



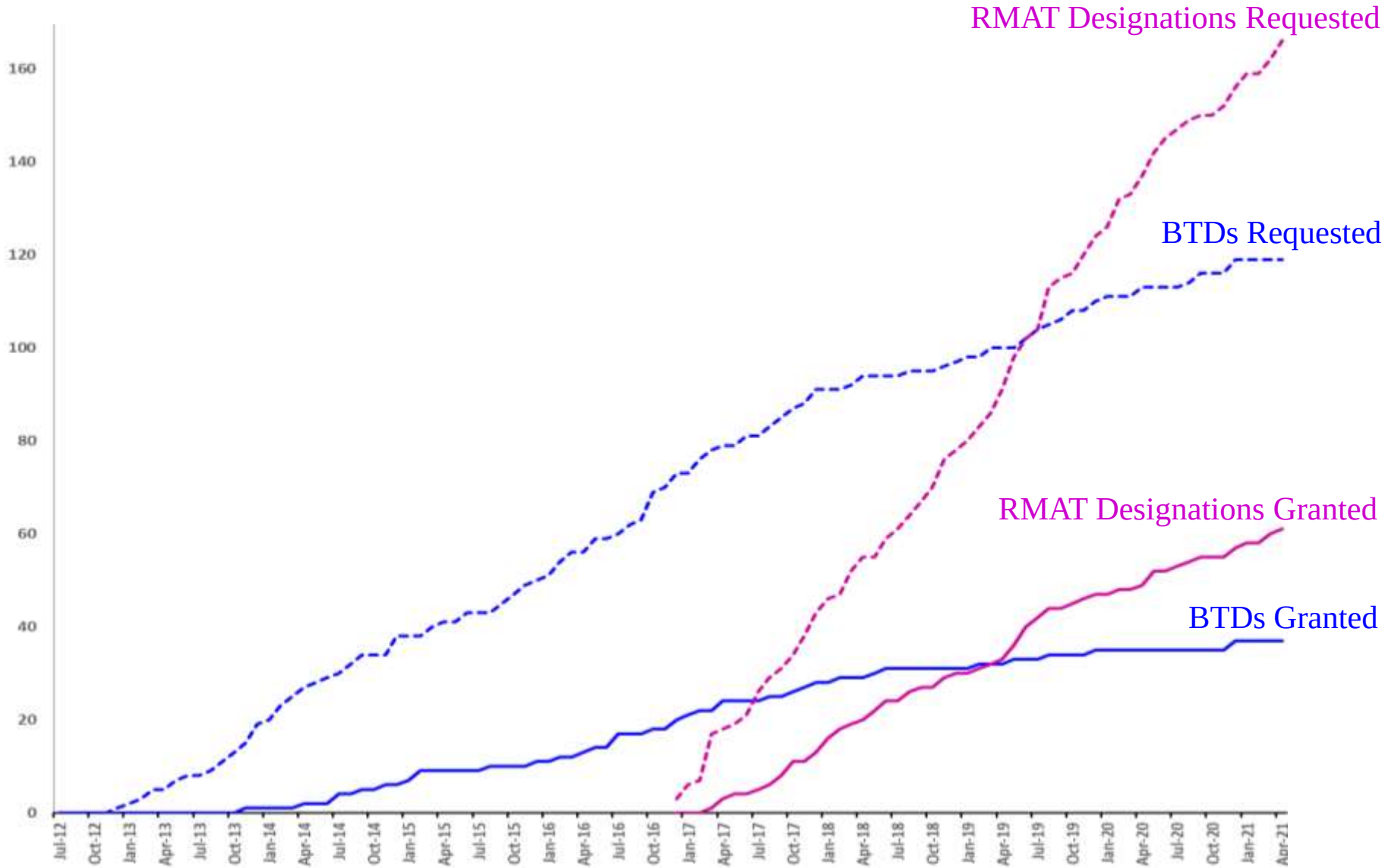
Annual Overview of RMAT Designation Requests (excludes withdrawn and pending requests)



Annual Overview of BTD and RMAT Designation Requests (excludes withdrawn and pending requests)



Cumulative Overview of BTD and RMAT Designation Requests (excludes withdrawn and pending requests)



Summary

- FDA has several programs to facilitate and expedite product development and review to address unmet needs for the treatment of serious/life-threatening conditions
  - Priority Review, Accelerated Approval, Fast Track Designation, Breakthrough Designation and Regenerative Medicine Advanced Therapy Designation
- Designation request can be submitted at the same time as the original IND or any time after
- Regenerative Medicine Advanced Therapy Designation is the newest of the programs and has garnered much interest for regenerative medicine therapies

Thank You

Acknowledgements

Dr. Xiaofei Wang

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FDA Headquarters

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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