

Blood Products Advisory Committee Meeting

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Overview

Office of Tissues and Advanced Therapies (OTAT) and Division of Plasma Protein Therapeutics (DPPT)

Basil Golding, MD

Director, DPPT

Site Visit for Plasma Derivatives Branch

April 22, 2021

Office of Tissues and Advanced Therapies (OTAT)

Office of Tissues and Advanced Therapies (OTAT)

OFFICE OF THE DIRECTOR
Wilson Bryan, MD
Rachael Anatol, PhD

DIVISION OF CELLULAR AND GENE THERAPIES
Raj Puri, MD, PhD
Stephen Oh, PhD

DIVISION OF PLASMA PROTEIN THERAPEUTICS
Basil Golding, MD
Mahmood Farshid PhD

DIVISION OF CLINICAL EVALUATION AND PHARMACOLOGY-TOXICOLOGY
Tejashri Purohit-Sheth, MD (Recruiting)

DIVISION OF HUMAN TISSUES
Scott Brubaker, MD
Ping He, MD

DIVISION OF REGULATORY PROJECT MANAGEMENT
Ramani Sista, PhD
Lori Tull, BS

- Cell Therapies Branch
- Gene Therapies Branch
- Gene Transfer and Immunogenicity Branch
- Cellular and Tissue Therapy Branch
- Tumor Vaccine and Biotechnology Branch

- Hemostasis Branch
- Plasma Derivatives Branch

- General Medicine Branch I
- General Medicine Branch II
- Pharmacology-Toxicology Branch I
- Pharmacology-Toxicology Branch II
- Oncology Branch
- Clinical Hematology Branch

- Human Tissue and Reproduction Branch

- Regulatory Project Management Branch I
- Regulatory Project Management Branch II
- Regulatory Project Management Branch III
- Regulatory Project Management Branch IV

Units that include lab research

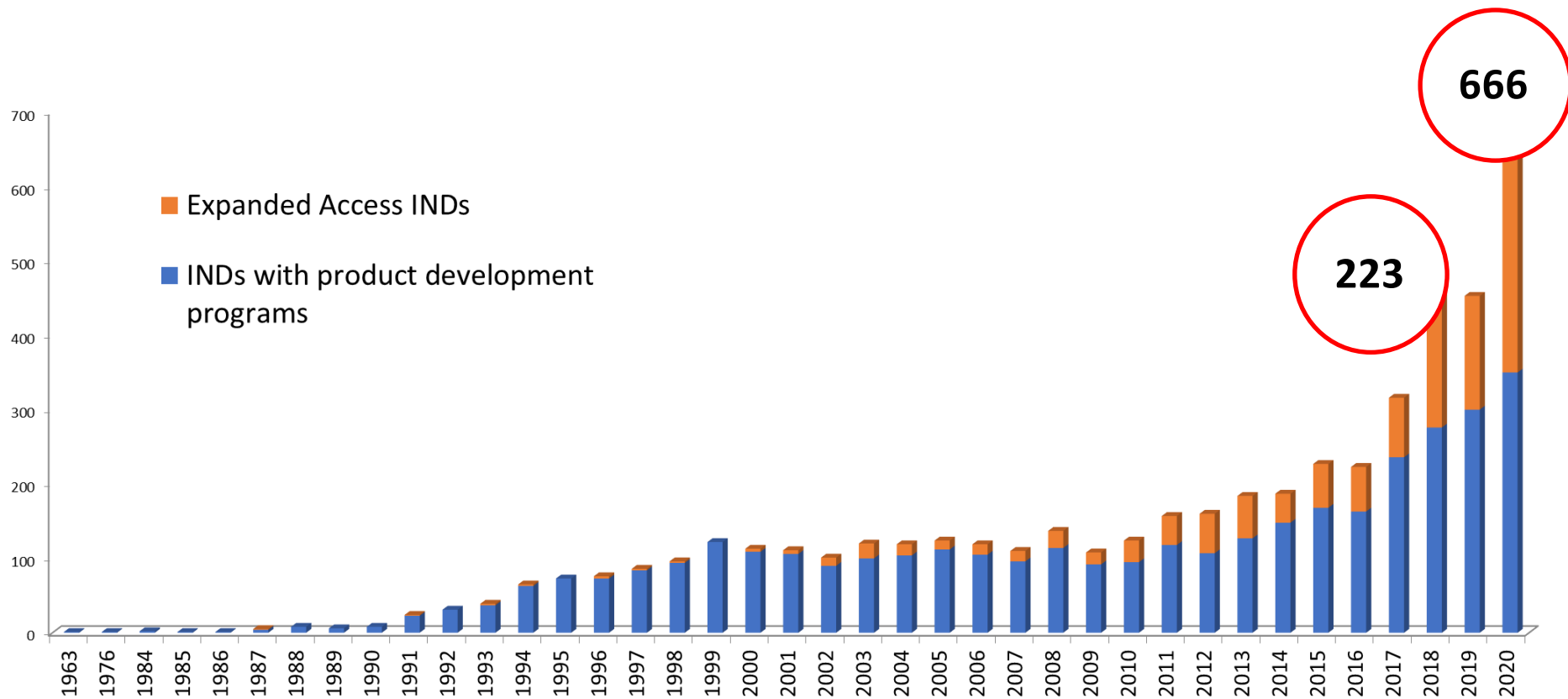
OTAT Products (non-DPPT).

- Stem cell and stem cell-derived products
 - Hematopoietic, mesenchymal, cord blood, embryonic, induced pluripotent stem cells (iPSCs)
- Terminally-differentiated cell therapies
 - Pancreatic islets, chondrocytes, myoblasts, keratinocytes, hepatocytes
- Therapeutic vaccines and other antigen-specific active immunotherapies
 - Cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies, peptides, proteins
 - Non-infectious disease therapeutic vaccines, such as peptides, proteins, small molecules

OTAT Products, Cont'd.

- Gene therapies
 - Genetically modified cells
 - Plasmids, viral vectors, bacterial vectors
- Xenotransplantation products
- Tissues and tissue-based products
- Some devices and combination products
 - Devices with a cellular component
 - Selected devices for the manufacture or delivery of cells
 - Donor screening tests (for use with cadaveric blood samples)

All OTAT INDS [i.e., Research and Expanded Access (EA)] 1963 – 2020



BLA Approvals in 2020 – 2021

- **SEVENFACT** coagulation factor VIIa (recombinant)-jncw
 - Treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors
- **TECARTUS** brexucabtagene autoleucel (CD19)
 - Relapsed or refractory mantle cell lymphoma
- **BREYANZI** lisocabtagene maraleucel (CD19)
 - Relapsed or refractory large B-cell lymphoma
- **ABECMA** idecabtagene vicleucel (BMA)
 - Relapsed or refractory multiple myeloma
- **RYPLAZIM** plasminogen
 - Treatment of plasminogen deficiency
- **STRATAGRAFT** – in vitro grown human skin
 - Treatment of burns
- **RETHYMIC** – in vitro processed and grown human thymic tissue
 - Treatment of athymic infants

BLA Supplements in 2020/Oct.2021

- Efficacy: 15/3
- Labeling: 28/16
- Manufacturing (non-devices):
284/266

Device Applications in 2020/Oct. 2021

- 510(k) Original Applications: 20/28
 - Clearances: 7/10
- IDE Original Applications: 17/18
- IDE Amendments: 244/220
- PMA Supplements: 18/35
- HDE Supplements: 7/18
- Qsub Submissions: 18/57

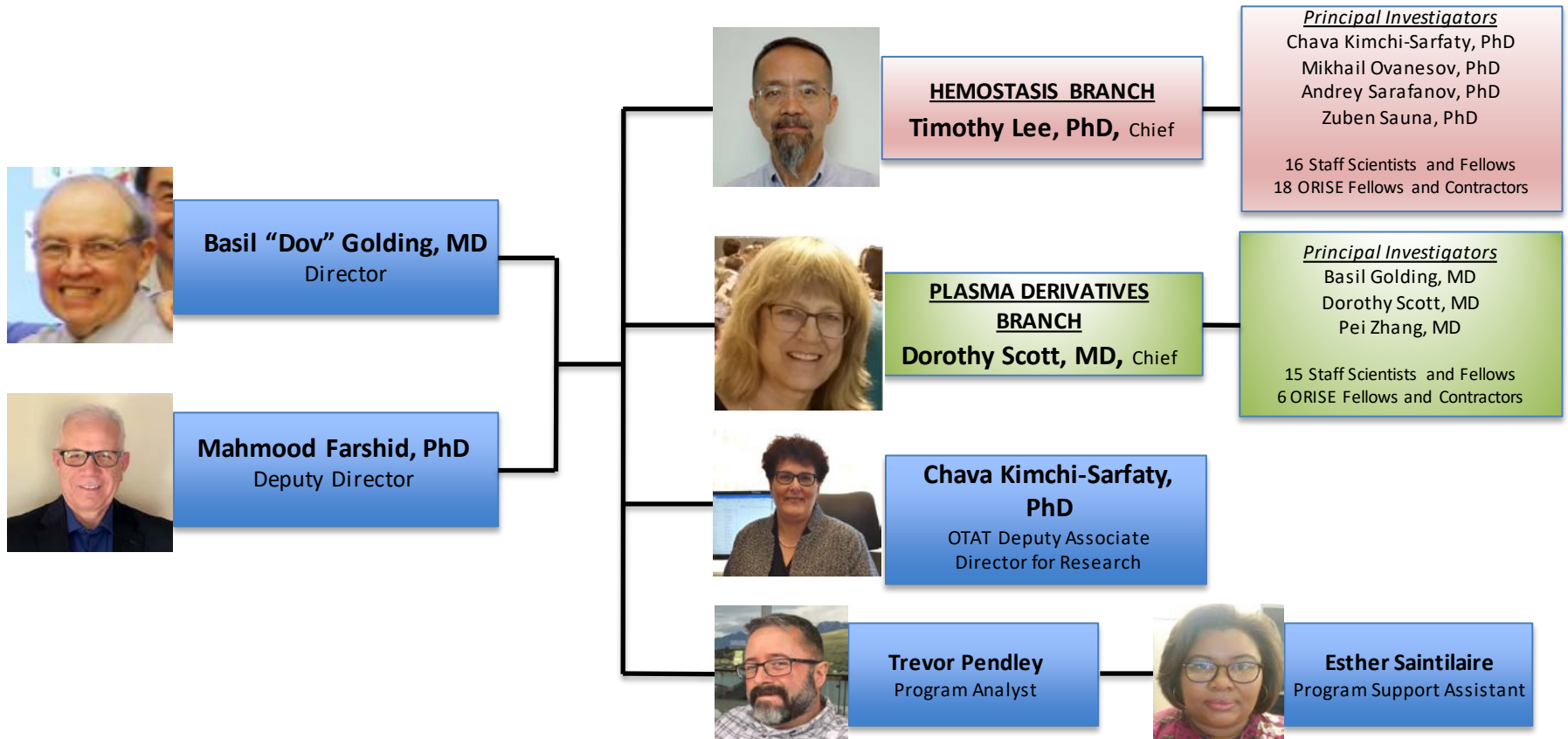
OTAT Regulatory Science



- 22 laboratories
- 31 publications in 2020
- 40+ external conference presentations
- 7 COVID – related research projects

Division Of Plasma Protein Therapeutics (DPPT)

Division of Plasma Protein Therapeutics - Organization



DPPT Workload (% of time)

	<u>Research</u>	<u>Review</u>
Regulatory Scientists (10)	0	100
PIs (7)	50	50
Research Scientists (20)	50	50
Staff Fellows (2)	50	50
ORISE & Contractors (24)	100	0

DPPT: Regulatory Function

- Applications and products
 - Biologics, drugs, and devices
 - Diverse complex proteins
- Evaluation process of products
 - Scientific review of manufacturing processes
 - Laboratory investigation if needed
 - Assay development
 - Standards are developed for lot release of different products and are often distributed as CBER and/or international standards
- Surveillance
 - Inspections
 - Adverse Event Reports
 - Product failures
- Legal Framework
 - CFR, PDUFA, MDUFMA, FD&C Act, PHS Act

DPPT: Other Tasks

- Policy and Guidance documents
- Harmonization: ICH guidance, EMA, Canadian Health Authority
- Liaisons:
 - Government Agencies (e.g., NIH, CDC)
 - Industry (PPTA)
 - Patient groups (NHF, IDF)
- Communications
 - Websites/Letters
- Workshops
- Scientific committees
- Citizen Petitions

Committees & Working Groups (1)

- Nat'l Institute of Biological Standards and Control (United Kingdom)
 - Procoagulant Activity of IGS, Study Group on Thrombin Generation Tests
 - SSC-ISTH Secondary Coagulation Standard Lot #5
 - New Factor VIII products with WHO International Standards
- WHO
 - Collaborative Study for the 2nd International Standard for Factor V and ADAMTS13
 - WHO 1st International Standard for TAFI, plasma
 - 1st International Standard for anti-SARS-CoV-2 antibody and Reference Panel
 - Reference reagent to standardize haemagglutination testing for anti-A & anti-B in serum and plasma
 - 3rd WHO international standard for anti-D immunoglobulin
 - Harmonization of thrombin generation assay used to assess the safety of plasma-derived products
- EDQM
 - European Pharmacopoeia Expert Group 6B

Committees & Working Groups (2)

- CBER, CDER, and other FDA components
 - FDA/CDER working group on umbrella container/closure system guidance, extractables & leachables sub-guidance
 - CBER Genomics Working Group
 - CBER HIVE Advisory Board
 - Business process committees, e.g. BRCC, IMCC, RMCC, LTS, CBER Safety, etc.
- Multiple USP Committees and Working Groups
- Multiple industry educational groups, e.g. PDA, CASSS, DIA

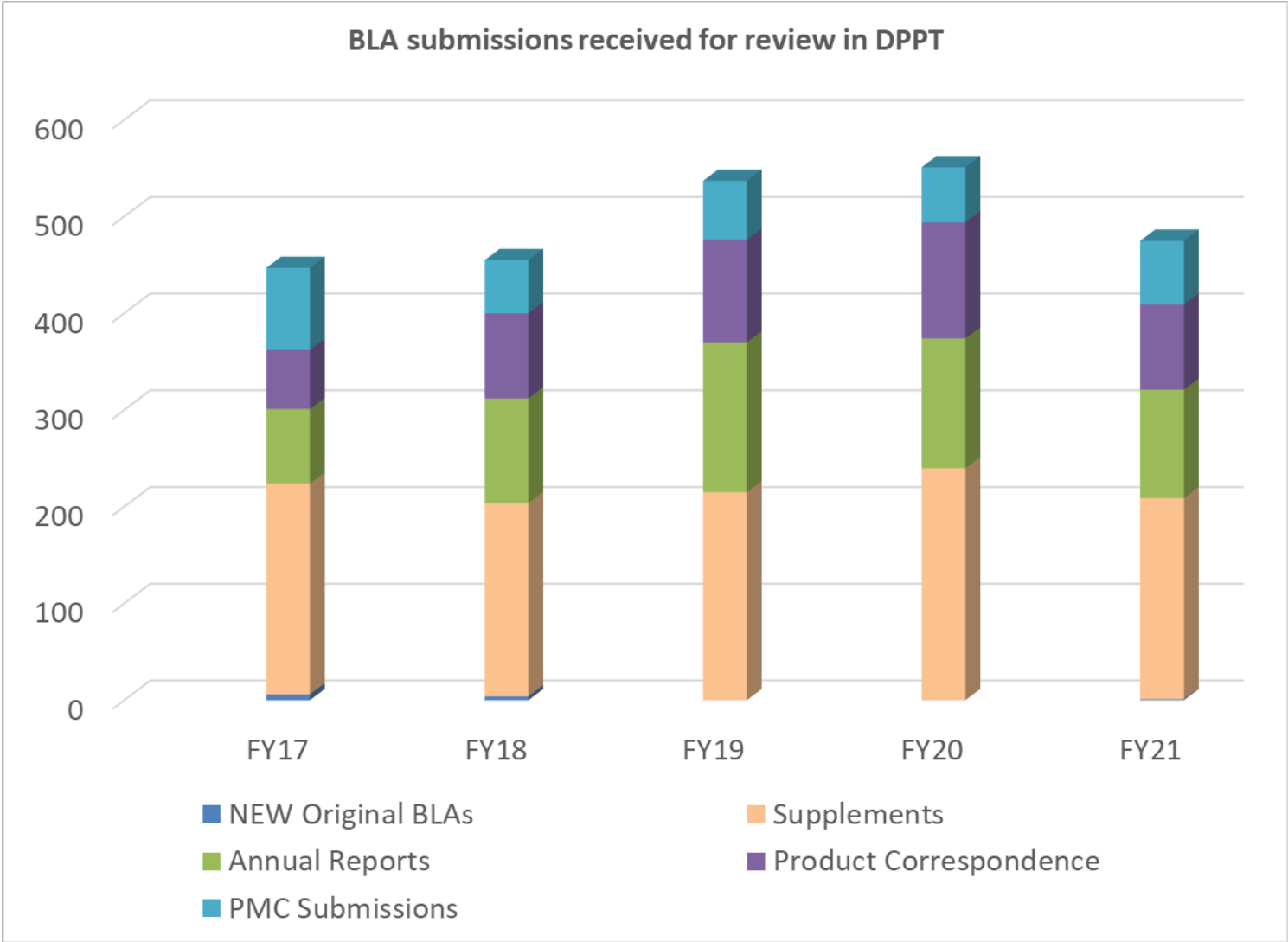
DPPT: Regulatory Process

Decisions - based on scientific data showing safety, efficacy and purity

– decision-making process

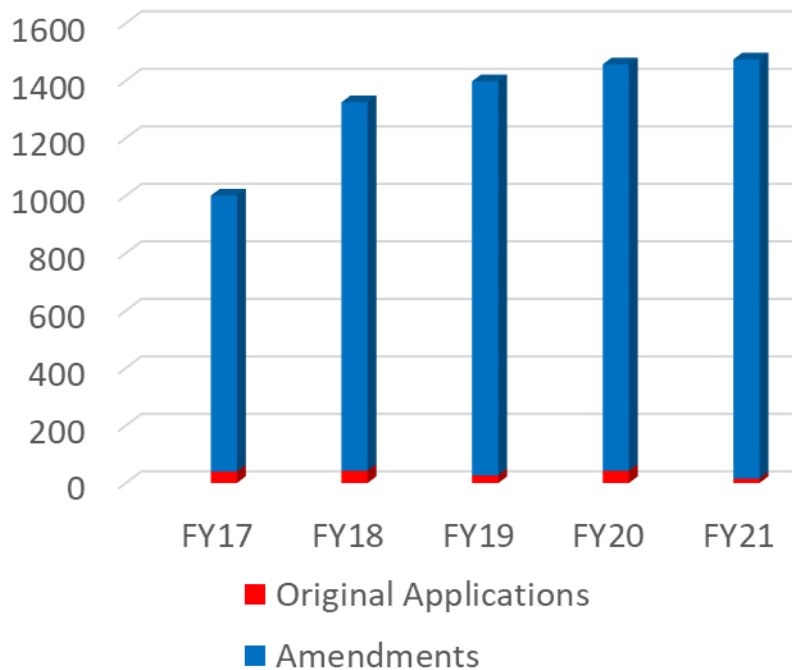
- internal review
- presentations to Advisory Committees
- meetings with manufacturers
 - Pre-IND/IDE
 - IND
 - Pre-BLA
 - Mid and Late Cycle Meeting

DPPT: BLA applications and supplements

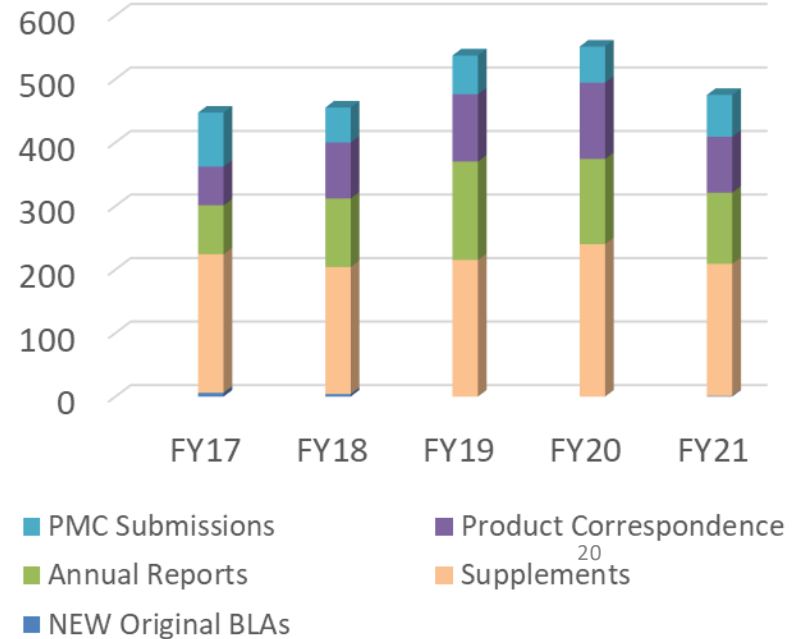


DPPT Regulatory Workload Metrics

IND/IDE/MF submissions received for review in DPPT



BLA submissions received for review in DPPT



Licensed Products- Plasma Derivatives Branch

- **Polyclonal Immune Globulins** (intravenous, subcutaneous, intramuscular) – for Primary Humoral Immunodeficiency, Idiopathic Thrombocytopenic Purpura, Multifocal Motor Neuropathy, Chronic Idiopathic Demyelinating Polyneuropathy, Kawasaki Syndrome, and prevention of recurrent infections in B-Cell Chronic Lymphocytic Leukemia, Dermatomyositis.
- **Specific Immune Globulins** – against Rabies, Tetanus, Hepatitis A, Hepatitis B, Cytomegalovirus, Anthrax, Infant Botulism, Varicella, Vaccinia, Rho(D).
- **Antitoxins** – for Botulism and for Digoxin poisoning.
- **Antivenoms** to treat envenomation by Pit Vipers (Rattlesnakes and related species), Coral Snakes, Black Widow Spiders, Arizona Bark Scorpion, Equine serum.
- **Anti-T cell therapies** for prevention or treatment of transplant rejection.
- **Alpha-1 Proteinase Inhibitor**, for treatment of pulmonary disease in A1PI-deficient patients.
- **C1 Esterase Inhibitor**, for treatment of Hereditary Angioedema.

- **Coagulation Factors**
 - Factors VIII and IX (Human plasma-derived & Recombinant)
 - von Willebrand Factor (Human plasma-derived & Recombinant)
 - Fibrinogen Concentrate
 - Factor X
 - Factor XIII (Human plasma-derived & Recombinant)
- **Anti-coagulants**
 - Protein C
 - Antithrombin III (Human plasma-derived & Recombinant)
- **Bypassing Agents**
 - Anti-Inhibitor Coagulant Complex
 - Recombinant activated Factor VII
- **Hemostatic Agents**
 - Thrombin (Bovine, Human & Recombinant)
 - Fibrin Sealant
 - CryoSeal FS System
 - Fibrin Sealant Patch
- **Reversal Agents for Anticoagulants**
 - Prothrombin Complex Concentrate
 - Recombinant Factor Xa Variant, Inactivated

Scope of DPPT Research

- Efficacy of Immune Globulin Products (Flu, Ebola, Zika, HCV and SARS-CoV-2)
- Study of the regulation of blood coagulation by coagulation Factors VIIa, IXa and XIa
- Aggregates in protein products
- Clearance mechanisms of Factor VIII and characterization of product-related impurities in recombinant Factor VIII products
- Immunogenicity: Fc-fusion proteins, Factor VIIa, and CRISPR/Cas9
- Pharmacogenomic and codon optimization studies of proteins
- Materno-fetal transfer of antibodies
- Assay and standard development
- Counter-terrorism and Pandemics (e.g. Influenza, COVID-19)

Publications & Presentations (PIs)

52 Publications & 84 Presentations in Jan. 2019-Oct. 2021

Publication Topics:

- Immune response to SARS-CoV-2 vaccine
- Fc-Fusion drugs
- Therapeutic protein immunogenicity
- HLA donor optimization
- Synonymous mutations

Journals:

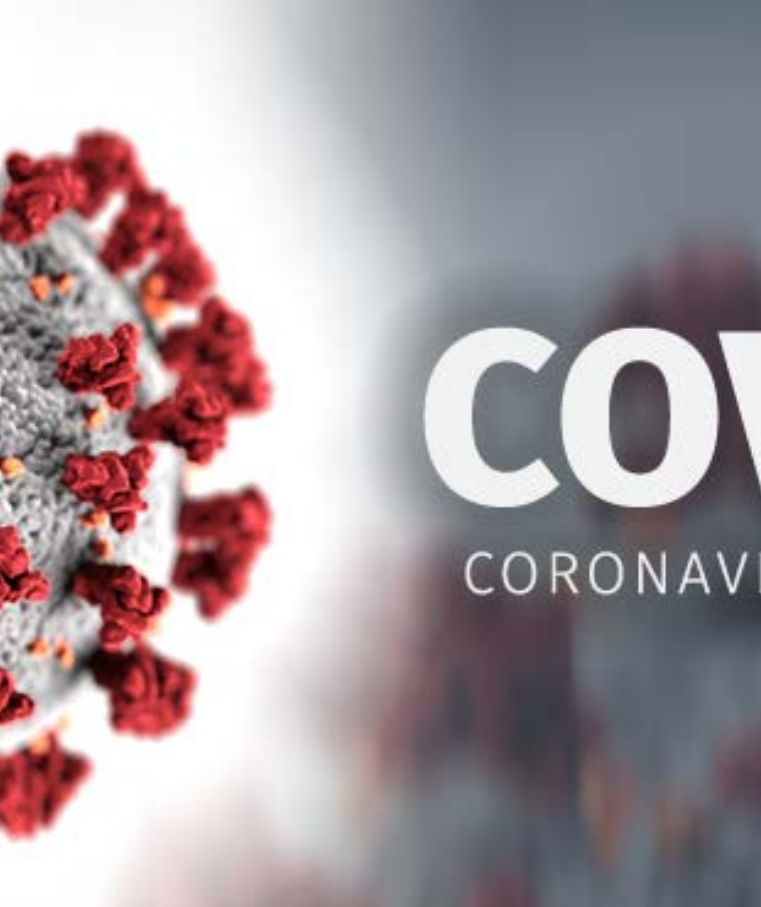
- PNAS
- Frontiers in Immunology
- Thrombosis and Haemostasis
- Molecular Biology
- Nature Communications
- International Journal of Medical Science
- Scientific Reports

Presentation Topics:

- Immune response to CRISPR
- Codon usage Bias
- Factor VIII characterization
- Influenza neutralizing antibodies
- Zika related birth defects

Meetings:

- Viral Safety and Viral Clearance Summit
- Plasma Protein Industry Summit
- American Society for Virology
- American Society of Hematology
- Int'l Society on Thrombosis and Haemostasis
- Drug Industry Association Annual



COVID-19

DPPT research addresses new challenges: COVID-19

- Dosing Considerations for Hyperimmune SARS-CoV-2 IG Based on Hamster Challenge Studies
- Investigating coagulopathies that are associated with mortality following SARS-CoV-2 infection
- Develop methods for rapid screening of convalescent plasma for SARS-CoV-2 neutralizing activity
- Design codon-modified versions of the SARS-CoV-2 virus to attenuate for vaccine use
- Testing of antibodies that neutralize SARS-CoV-2
- Examine binding of coagulation-related proteins to SARS-CoV-2

Outside Recognition of the Importance of DPPT Research

Projects received FDA or external grants (since 2017):

- BARDA
- OCET Zika Supplemental
- FDA Challenge Grant-Chief Scientist
- FDA Challenge Grant-NanoCores
- FDA Challenge Grant-MCMi
- FDA/NCTR Perinatal Health Center of Excellence
- OCET COVID-19 Supplemental

Projects received CRADA agreements:

- Boston Children's Hospital
- Cleveland State University (based on RO1)

Looking ahead

DPPT has identified and has plans to address the following gaps in regulatory research:

- Bioinformatics approaches to examine immunogenicity and introducing DNA sequence changes for optimizing product yield
- Next generation immune globulins (IGs), such as recombinant polyclonal IGs, modified IGs, and novel IGs against emerging pathogens and toxins
- Safety issues related to platform technologies for protein modifications such as Fc and albumin fusion and pegylated proteins

Anticipated New Products (1)



- **Proteins with Improved pharmacological properties**
 - New recombinant coagulation factor variants
 - New PEGylated coagulation factors
 - New fusion proteins of coagulation factors, e.g., with XTEN or CTP
- **Plasma-derivatives & their recombinant analogs for factor deficiencies & other disorders in hemostasis**
 - Coagulation Factors as replacement therapy for deficiencies
 - Heme scavengers for the treatment of Sickle Cell Disease
 - Recombinant variants for the treatment of arterial thrombosis and thromboembolism
 - Reversal agents for anticoagulants
 - Metalloprotease to treat TTP

Anticipated New Products (2)

- **HDL**
 - For the reduction of atherothrombotic events in patients with acute coronary syndrome who are at high-risk of recurrent ischemic events
- **Immune Globulins (IG)**
 - COVID-19 IG made from human plasma
 - Recombinant polyclonal immune globulins
 - Glycosylation variants
 - Human hyperimmune polyclonal antibodies sourced from transchromosomic animals, e.g. anti-SARS-CoV-2, anti-influenza IG
 - Oral milk or colostrum-derived bovine Immune Globulin treatments for gastrointestinal diseases
 - New equine-derived antitoxins (loxoceles, coral snake, black widow spider)
- **Serine Proteases**
 - Recombinant products
 - Subcutaneous formulations
 - Inhalational formulations

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- Upper Management
- DPPT Staff

Thank You!