Project Orbis Update

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FDA Oncology Center of Excellence (OCE)

Office of Tissues and Advanced Therapies (OTAT)

- CAR-T and other cellular therapies, gene therapy, therapeutic vaccines

Office of Oncologic Diseases (OOD)

- small molecules, monoclonal antibodies, antibody-drug conjugates

- Established on January 20, 2017
- Authorized by 21st Century Cures Act: First FDA Inter-Center Institute

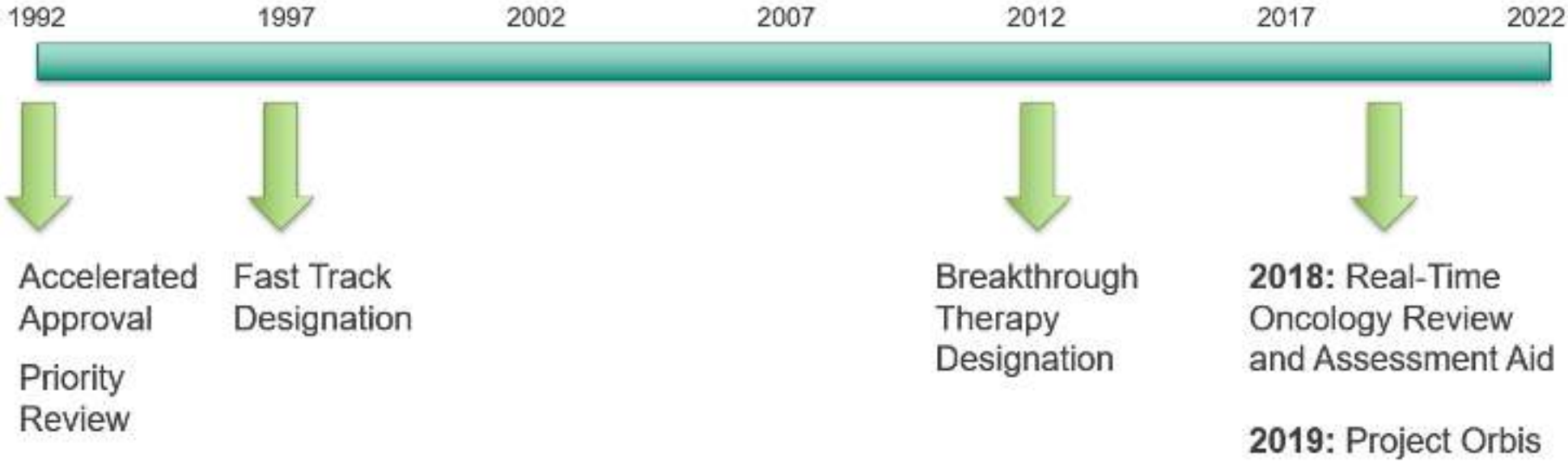
Office of In Vitro Diagnostics and Radiological Health

- companion and complementary diagnostics

Approvals since 20 Jan 2017:
76 new molecular entities (NME)
185 new indications
Average review time ~ 6 months

FDA Expedited Programs	Fast Track	Breakthrough Therapy	Priority Review	Accelerated Approval
Program	Designation	Designation	Designation	Approval Pathway
Qualifying Criteria (all require condition to be <u>serious</u>)	• Nonclinical or clinical data demonstrate potential to address unmet need	• Preliminary clinical evidence demonstrates substantial improvement over available therapies	• If approved would result in significant improvement in safety or efficacy	• Demonstrates effect on endpoint reasonably likely to predict clinical benefit over available therapies
When to Submit	IND or after	Ideally no later than EOP2	With (s)BLA, (s)NDA	Discuss during development
Features	• Expedite development and review • Rolling review	• Intensive development guidance • Organizational commitment • Rolling review	• (6) 8 month vs. (10) 12 month review clock for regulatory action	• Approval based on effect on endpoint that is reasonably likely to predict clinical benefit

Historical Context of FDA and OCE Programs



FDA Oncology Metrics:

- **Accelerated Approval:** 84% of FDA accelerated approvals from 2010-2019 were for oncology indications
- **Priority Review Designation** (2015-2020) for oncology approvals: 88% of NME approvals, 82% of efficacy supplement (new indication) approvals
- **Breakthrough Therapy Designation** (2020): 43% of CDER BTDs for oncology indications

Summary of OCE Review Programs

	Real-Time Oncology Review (RTOR)	Assessment Aid	Project Orbis
Start Date	February 2018	April 2018	May 2019
Objective	Increase efficiency of review through earlier submission of critical efficacy and safety data	Focus review on critical assessment, decrease administrative time	Facilitate faster patient access to innovative cancer therapies in participating countries
Key Elements	Early submission of datasets	Template with distinct sections for data, Applicant position and FDA Assessment	Direct collaboration between FDA and partner countries
Qualifying Criteria	Substantial improvement over available therapy Straightforward study designs and well-understood endpoints	Any oncology drug application	High impact and clinically significant applications

FDA Oncology Global Collaboration

- Began in October 2004 with European Medicines Agency (EMA)
- **Expanded Oncology Cluster to other Regulatory Authorities:**
  - January 2010: Health Canada (HC)
  - January 2014: Pharmaceuticals and Medical Devices Agency (PMDA) (Japan)
  - July 2014: Therapeutic Goods Administration (TGA) (Australia)
  - July 2016: Swissmedic (SMC) (Switzerland)
- **Project Orbis:** Collaborative Review Program
  - Launched in May 2019
  - Current participating countries (Project Orbis Partners): Australia, Brazil, Canada, Israel, Singapore, Switzerland, United Kingdom

Requirements for Project Orbis Countries

- Confidentiality agreement with all other Orbis countries
- Application submission in English language with Sponsor authorization letter to share information across Orbis countries
- Availability to participate in meetings
  - Product-Specific
  - General: Quarterly

Project Orbis Overview

- **Application Selection Process**: FDA serves as primary coordinator. Plan for concurrent or near-concurrent submissions across participating countries
  - **Assessment Aid:** primary review document for FDA and core reference document for Orbis countries
- **Review:** multi-country teleconferences (2-3 per application)
  - each country retains full independence in regulatory decision and labeling negotiations
- **Project Orbis Types:** Type A-C, classified according to submission gap to FDA timeline

Project Orbis Types

		Sharing of AAid	Multi-country teleconferences	Concurrent review with FDA	Concurrent action with FDA
Type A	Regular Orbis	Yes	Yes	Yes	Yes
Type B	Modified Orbis	Yes	Yes	Possible	No
Type C	Orbis Written Report Only	Yes	No	No	No

Key Features of Project Orbis

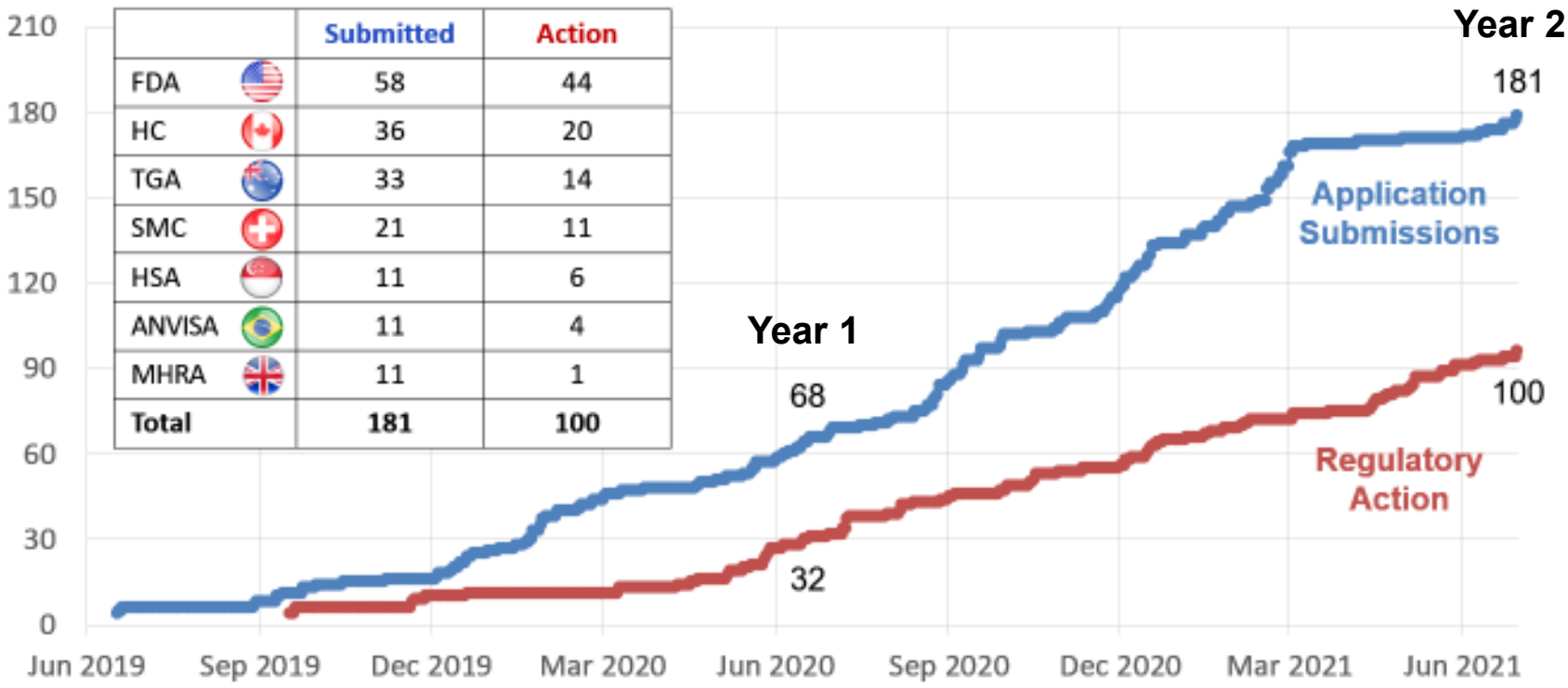
- **Leverages FDA staffing and expertise with application review**
  - **FDA Oncology Staff:** 250+ full-time (100 oncologists + 10 clinical analysts, 30 statisticians, 30 clinical pharmacologists, 30 nonclinical, 70 project managers)
  - **FDA Disease-Specific Teams**: 17

Breast-Gynecologic (2)	Genitourinary (2)	Thoracic/Head-Neck (2)
Gastrointestinal (2)	Melanoma/Sarcoma	Pediatric/Neuro-oncology (2)
Leukemia/Transplant (3)	Lymphoma (2)	Myeloma

  - FDA review provides for independent multi-disciplinary assessment including full review of datasets.
- **Not a work-sharing initiative**
- **Each country retains independent decision-making for each application**

Project Orbis 2-Year Update

	Submitted	Action
FDA	58	44
HC	36	20
TGA	33	14
SMC	21	11
HSA	11	6
ANVISA	11	4
MHRA	11	1
Total	**181**	**100**



Additional Highlights:

1. Submission gap to FDA continues at median of 1 month.
2. Regulatory action gap varies according to Project Orbis type (overall median 2.6 months).

Project Orbis Year 2

Workload

- 2-fold increase in Year 2 submission workload compared to Year 1
- Increase in proportion of Type B (37%) and Type C (20%)
- NMEs comprise 32% of workload
- ~ 1/3 of FDA oncology workload referred to Project Orbis

Process Changes

- Orbis teleconferences changed to issue-based discussion format
- Reduced number of meetings (1-2 for supplements, 2-4 for NMEs)
- Assessment Aid shared at conclusion of FDA review

Project Orbis

Challenges

- Future expansion to other countries
- Co-approval with diagnostic tests
- Advanced therapies