Association of Graduate Regulatory Educators

Education Webinar Topics

Project Orbis: Global Collaborative Review Program

and the TGA International Collaboration and Reliance Regulatory Pathways

Speakers: Dr. Kaye Robertson and Dr. R. Angelo de Claro

June 23/24, 2021

AGRE Global

- Initiated in 2010 through a series of meetings
- Brought together leaders of programs offering graduate training in regulatory affairs and regulatory science that developed a formal organization with several goals:
  - to share best practices in regulatory education and promote the continued development of regulatory education as an academic discipline
  - to provide a forum for discussion of issues of mutual importance for educating stakeholders involved with commercializing products or services in the biomedical product and healthcare industries
  - to support the development of an organizational critical mass that is well-positioned to impact public policies that affect regulatory education in the US and internationally

- **AGRE** is a place to meet and exchange ideas with other regulatory educators internationally.
- **AGRE** is a forum for coordinating input on policy issues of importance to our educational programs.
- **AGRE** is a group that develops and consolidates teaching materials to make your teaching more effective.
- **AGRE** is a community for research on competencies, advancement of the discipline, and development of the profession.

- New members WELCOME (see website agreglobal.org)

Today's Webinar Speakers Bios

- **Dr. Kaye Robertson Australian Government Department of Health,Therapeutic Goods Administration (TGA)**
  - Dr Robertson is the acting Section Head of the Clinical Evaluation Section C (Oncology and Haematology) of the Prescription Medicines Authorisation Branch of the TGA. Dr Robertson is a Medical Officer with post graduate qualifications in epidemiology and clinical toxicology. She has an interest in international collaboration and actively contributes to the TGA – Australia Department of Foreign Affairs and Trade (TGA-DFAT) Indo-Pacific Regulatory Strengthening Program (RSP) that works with national regulatory authorities in lower resource contexts in the South East Asian region.
  - .

- **Dr. R. Angelo de Claro US Food and Drug Administration**
  - Dr. de Claro is currently the Associate Director (Acting) for Global Clinical Sciences with US FDA Oncology Center of Excellence (OCE). In this role, he leads OCE efforts to advance cancer drug development and regulatory science across the globe. Dr. de Claro is also the Division Director for Division of Hematologic Malignancies I with Office of Oncologic Diseases. He completed his Hematology-Oncology fellowship at University of Washington and Internal Medicine residency at Baylor College of Medicine. He has been with FDA since 2010.

SAVE the DATE
AGRE Annual Summit Meeting

- **September 12, 2021**
  - Free and open to all-registration is required to obtain ZOOM link
  - Time: 10am-2pm EST
  - **Topics to include**
    - Regulatory Industry Needs Now & Future-Industry panel
    - Creating a LinkedIn Profile from a Recruiter's Eye
    - Regulatory Has Talent – Recent Graduate Panel
    - Regulatory Writing Tips

AGRE Webinar
June 23, 2021

U.S. FOOD & DRUG ADMINISTRATION

Project Orbis: Global Collaborative Review Program

R. Angelo de Claro, MD

Associate Director (Acting) for Global Clinical Sciences
Oncology Center of Excellence

Division Director, Division of Hematologic Malignancies I
Center for Drug Evaluation and Research

U.S. Food and Drug Administration

For questions, please contact ProjectOrbis@fda.hhs.gov

Disclosures

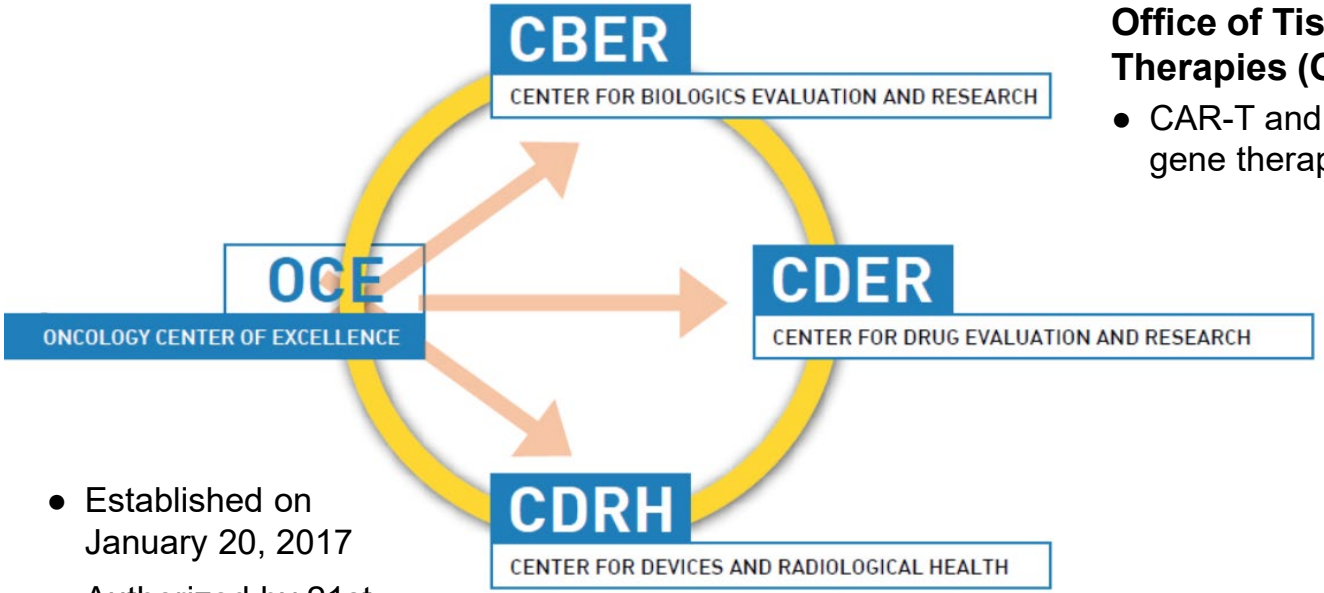
- Nothing to disclose
- This presentation represents the views of the speaker and should not be construed to represent official FDA policy.

Outline

- Oncology Center of Excellence (OCE) and Global Collaboration
- Project Orbis Framework
- Project Orbis 1-year Update
- Challenges and Future Directions

FDA Oncology Center of Excellence (OCE)

The Oncology Center of Excellence fosters unified interaction between 3 FDA centers



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 Invitro Diagnostics and Radiological Health

- companion and complementary diagnostics

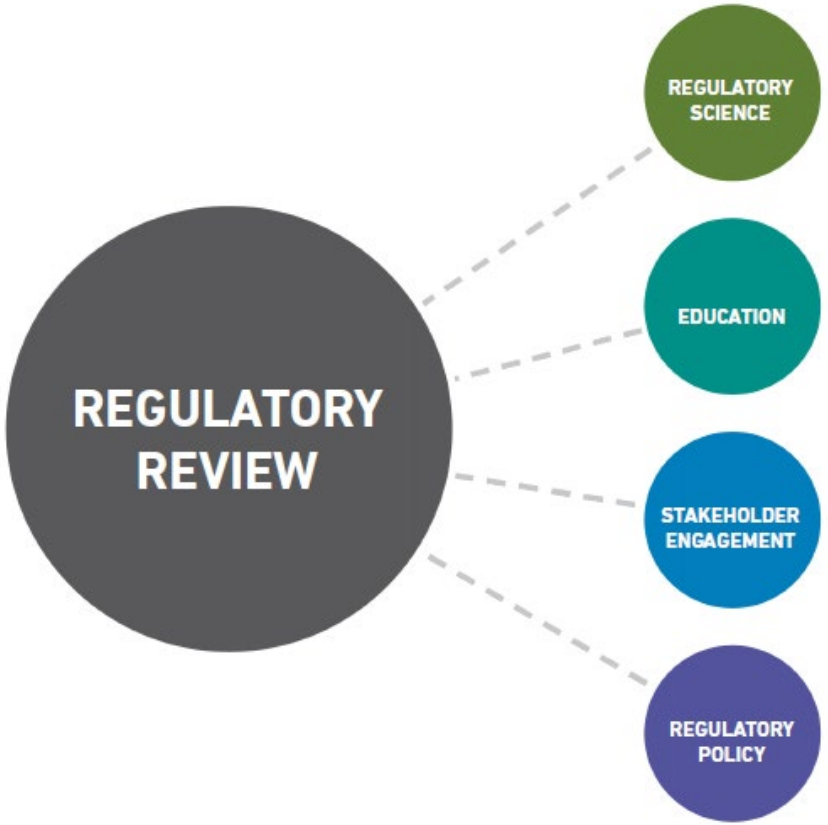
FDA Oncology Center of Excellence (OCE)

Mission

The mission of the OCE is to achieve patient-centered regulatory decision-making through innovation and collaboration.

Vision

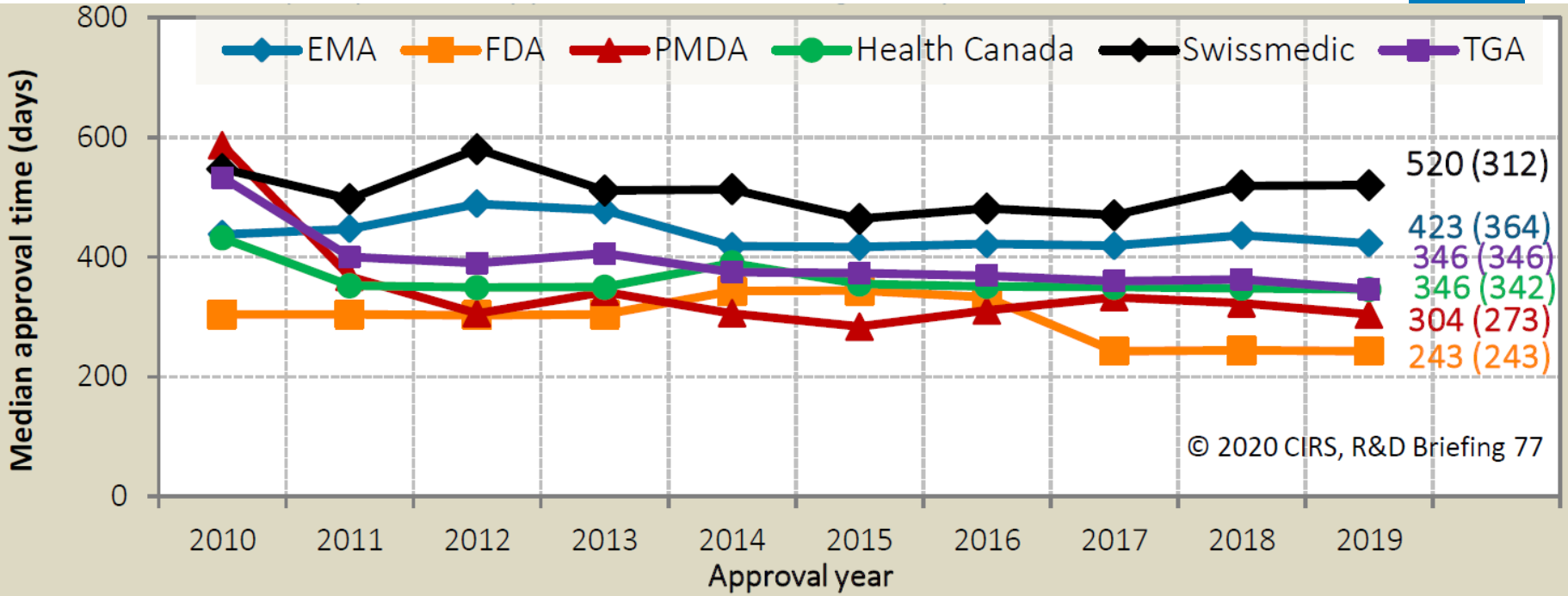
We seek to create a unified and collaborative scientific environment to advance the development and regulation of oncology products for patients with cancer.



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)
  - July 2014: Therapeutic Goods Administration (TGA)
  - July 2016: Swissmedic (SMC)
- **Project Orbis:** Collaborative Review Program
  - Launched in May 2019
  - Current participating countries (Project Orbis Partners): Australia, Brazil, Canada, Singapore, Switzerland, United Kingdom

New molecular entity median approval times for six regulatory authorities (2010-2019)



Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = median approval time for products approved in 2019; (N2) = median time from submission to the end of scientific assessment (see p.26) for products approved in 2019.

Reference: https://cirsci.org/wp-content/uploads/2020/06/CIRS-RD-Briefing-77-6-agencies.pdf
(Centre for Innovation in Regulatory Science)

Requirements for Project Orbis Countries

- Confidentiality agreement with all other Orbis countries
  - USA, Canada, Australia, Switzerland, Singapore, Brazil, UK
- Application submission in English language with Sponsor authorization letter to share information across Orbis countries
- Availability to participate in meetings
  - Product-Specific (per application): 3-5 for original applications, 2-3 for supplements/variations
  - General: Quarterly

Project Orbis Application Selection

- **Criteria**
  - high-impact, clinically significant applications, should generally qualify for priority review (US)
- **Application Selection Process**
  1. FDA or US Sponsor identifies application of interest
  2. US Sponsor submits Project Orbis submission plan (submission schedule per country, name and contact information for Sponsor affiliates)
  3. FDA sends submission plan to Project Orbis Partners (POP) to confirm interest and availability (allow at least 2-4 weeks for POP response)
  4. FDA confirms Orbis submission plan with US Sponsor

Application Review

- **Review Process**
  - FDA review: unchanged (filing meeting, midcycle meeting, labeling meetings, NME program meetings)
  - multi-country teleconferences
    - kickoff meeting, Project Orbis meetings (2-3 for supplements, 3-5 for new molecular entities)
  - information requests discussed with other countries
  - not a work-sharing initiative
  - each country retains full independence in regulatory decision and labeling negotiations

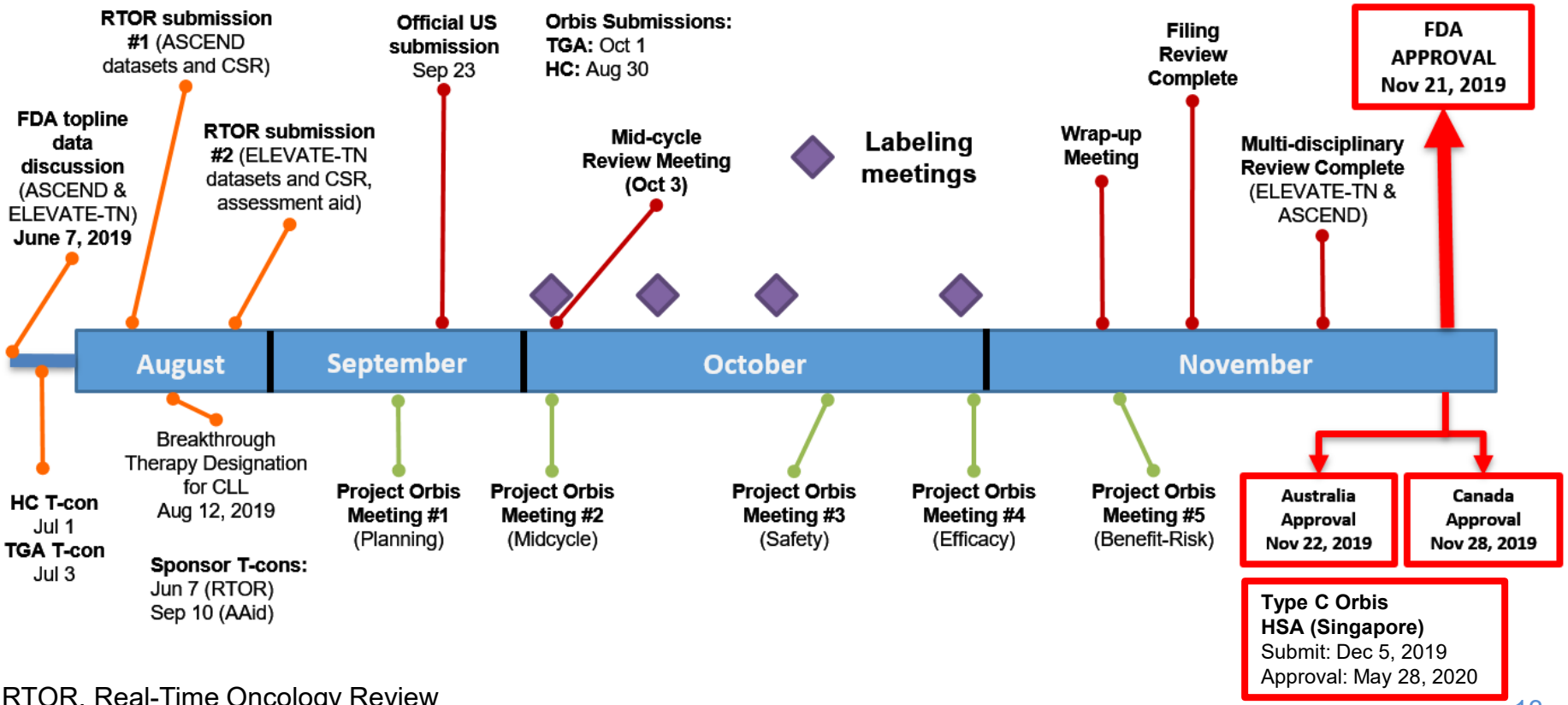
Project Orbis Review Document

- **Multi-disciplinary Review Document (Assessment Aid)**
  - Certain sections (background, nonclinical, clinical pharmacology, clinical trial description, efficacy, and safety) divided into 3 parts
    1. Data (completed by Applicant)
    2. The Applicant's Position (completed by Applicant)
    3. FDA Assessment / Regulatory Authorities Assessment
  - Overall Benefit-Risk and Final Recommendation
- **For NME/NAS (small molecule)**: CMC Assessment Aid
    1. Applicant Section
    2. FDA Assessment

Project Orbis Submission Types

		Concurrent submission with FDA	Sharing of FDA reviews	Multi-country Meetings	Concurrent review with FDA	Concurrent action with FDA
Type A	Regular	Yes	Yes	Yes	Yes	Yes
Type B	Modified	Possible	Yes	Yes	Possible	No
Type C	Written Report Only	No	Yes	No	No	No

Example: Acalabrutinib for CLL/SLL

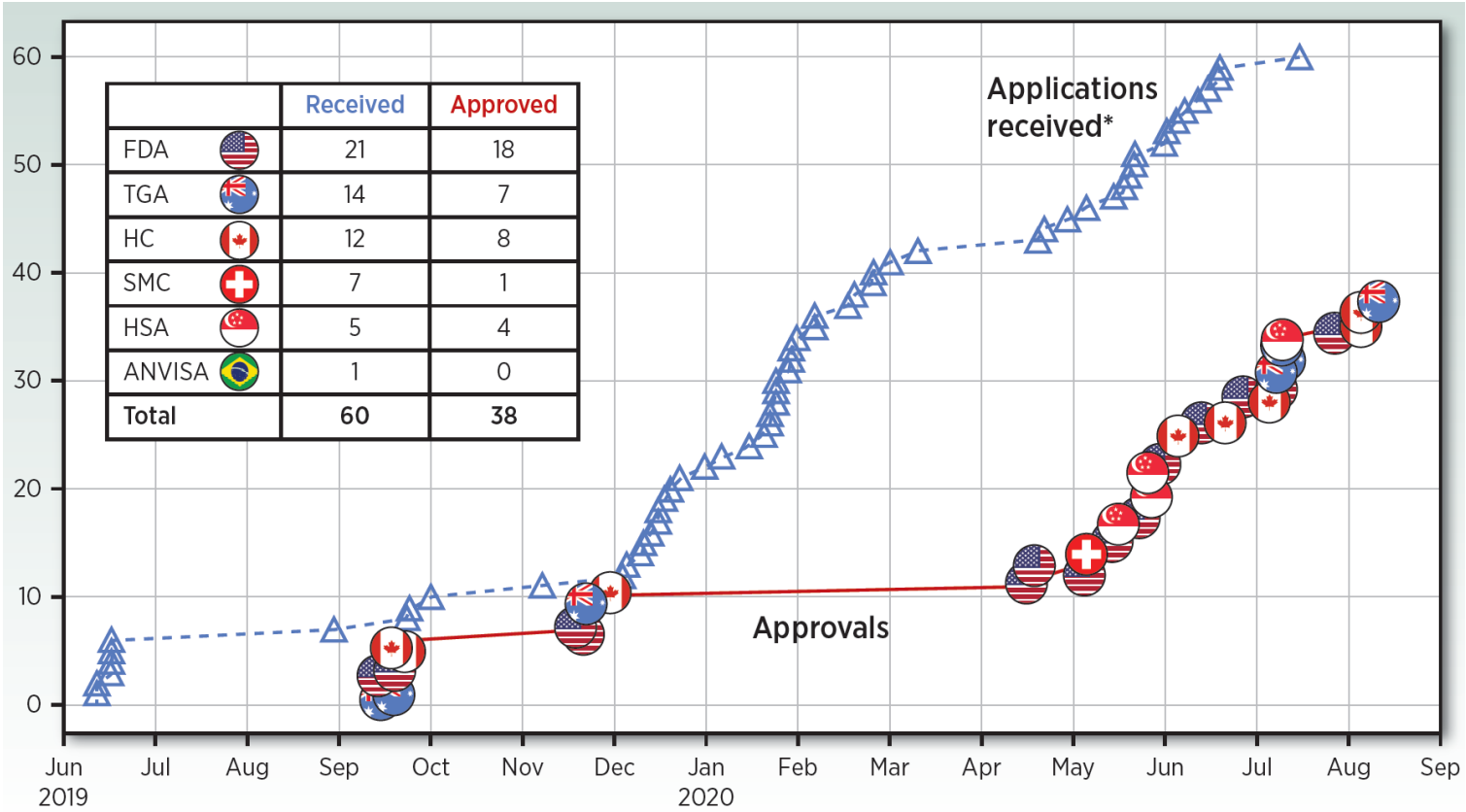


RTOR, Real-Time Oncology Review

Project Orbis 1-Year Update

- Application submissions (N=60)
  - Efficacy supplements/Type II variation: 72%
  - New molecular entity/New active substance: 28%
- Integration with other FDA or OCE Programs
  - Real-Time Oncology Review: 71%
  - Breakthrough Therapy Designation: 62%
  - Priority Review: 100%
  - Accelerated Approval: 29%
- Orbis country participation (including USA)
  - Median number per application of 3 (range: 2 to 5)

Project Orbis 1-Year Update



	Received	Approved
FDA	21	18
TGA	14	7
HC	12	8
SMC	7	1
HSA	5	4
ANVISA	1	0
Total	**60**	**38**

Additional Highlights:

1. Median time gap for submission: 0.6 m (range -0.8 to 9.0m)
2. Median time gap for approval: 1.1m (range 0.0 to 3.8m)
3. Orbis Types:
   - A (70%)
   - B (15%)
   - C (15%)

Reference: de Claro RA et al. *Clin Cancer Res.* 2020 Dec 15;26(24):6412-6416.

*Initial set of Orbis applications based on 21 FDA applications received from 12 Jun 2019 to 12 Jun 2020.

Project Orbis Challenges

- **Resource-intensive**
  - **Regulatory authorities**: review coordination and logistics (e.g., multiple time zones)
  - **Applicants/Sponsors**: concurrent submission and management of applications
- **Differences in regulatory and reimbursement framework across Orbis countries**

Future Directions

- Applied to broad range of oncology marketing applications (NME vs supplement, solid tumor and hematologic malignancies, small molecule and biologics)
  - Possible expansion to other applications (?): advanced oncology therapies, non-oncology indications
  - Project Orbis expansion to include other countries

For questions, please contact ProjectOrbis@fda.hhs.gov

Australian Government
Department of Health
Therapeutic Goods Administration

TGA International Collaboration and Reliance Regulatory Pathways

Dr Kaye Robertson
Medicines Regulation Division
Therapeutic Goods Administration

24 June 2021

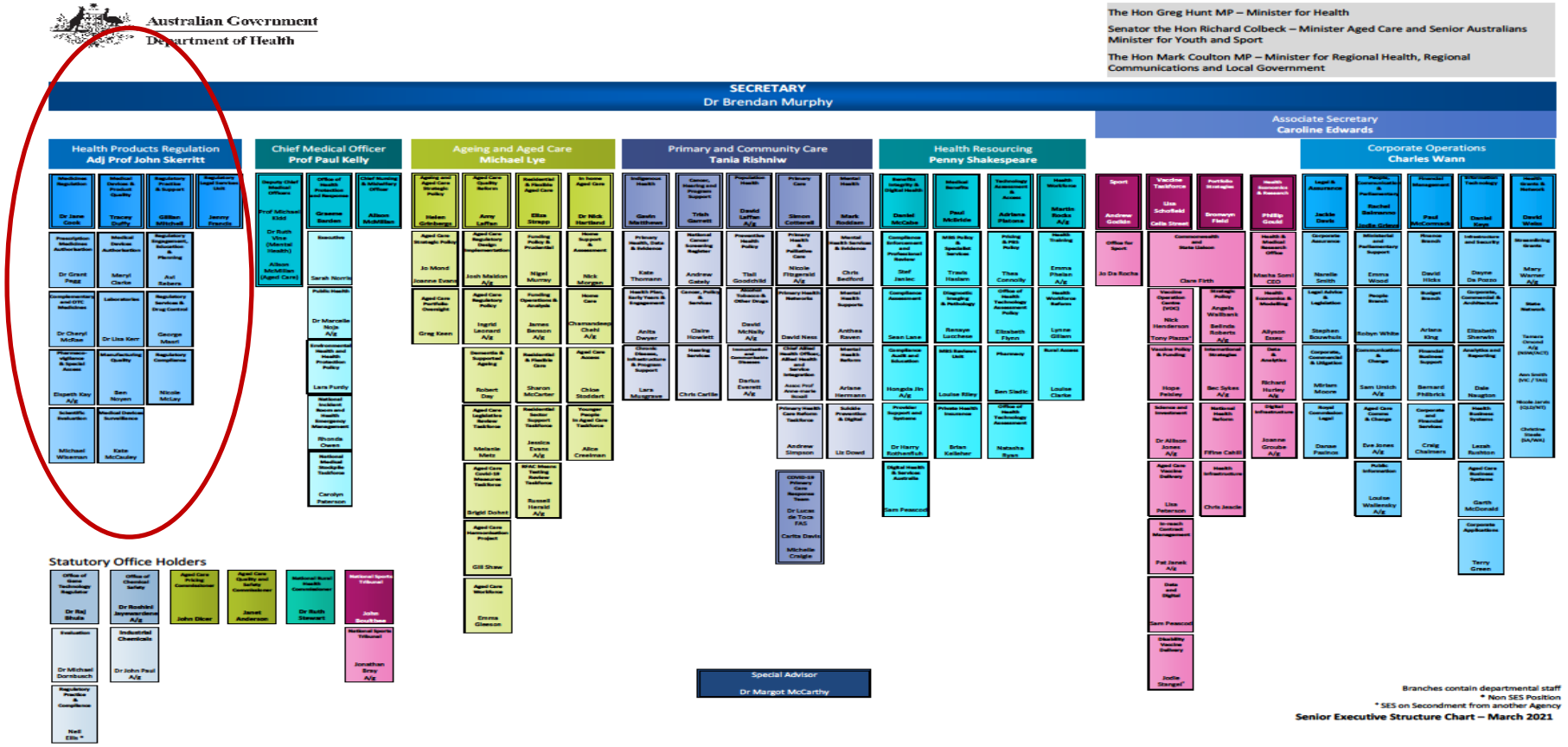
TGA Health Safety Regulation

Therapeutic Goods Administration

- Australian regulator of medicines and medical devices

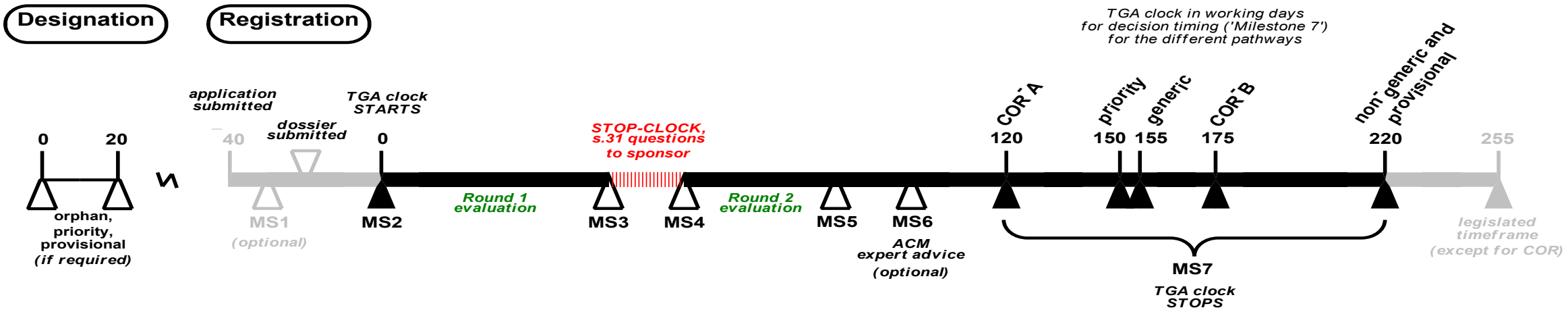
- Legislative basis:
  - *Therapeutic Goods Act 1989*
  - *Therapeutic Goods Regulations 1990*
  - *Therapeutic Goods Regulations (Medical Devices) 2002*

Australian Commonwealth Department of Health



TGA prescription medicine registration pathways

Snapshot: designations and pathways



2017

Orphan drug reforms final

Priority pathway

2018

Provisional pathway

Comparable Overseas Regulator (COR) pathway

Access work-sharing

2019

Project Orbis (FDA)

Expanding our work with international partners

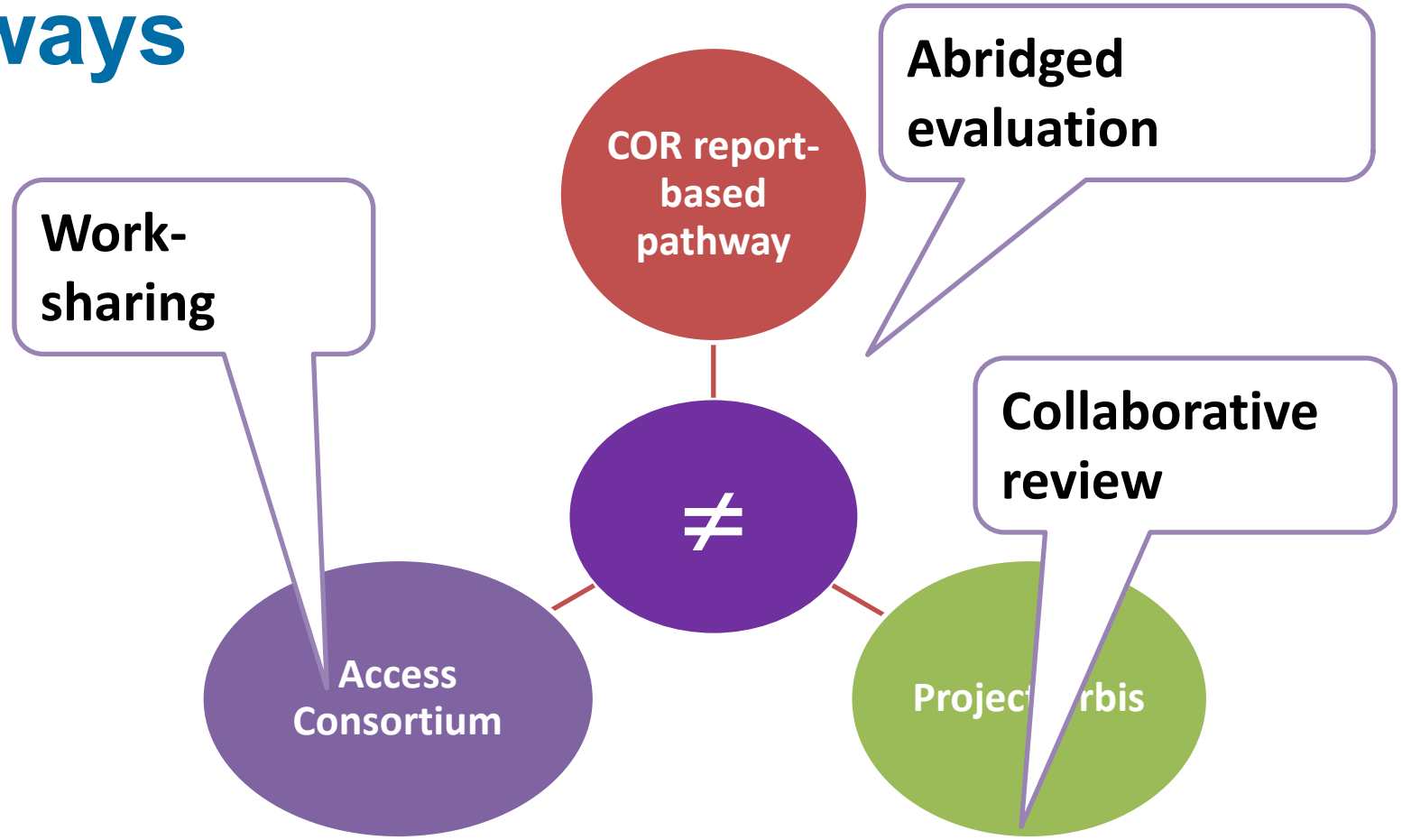
- Australian Government commitment to improve access and accessibility to prescription medicines

- The key pillars of the TGA's International Engagement Strategy include:
  - Ensure TGA reflects international best practice
  - Increase efficiency in regulatory processes
  - **Participate in work sharing, information sharing, and regulatory convergence activities.**

TGA reliance pathways

Key principles:

- TGA sovereignty over decision making
- Reliance **does not** represent a less robust form of regulation
- Regulators we work with have similar values and approaches to critical decision-making
- Reliance provides flexibility to TGA/applicants and can be tailored to the needs of the regulatory system



Industry's support and adherence to these principles is vital to the success of these pathways

Project ORBIS, the Australian perspective

- Global collaborative review program for oncology drug applications
  - new drugs
  - new indications

- Key features:
  - Parallel/collaborative review of the dossier
  - Use of Common Review Document (Assessment Aid)
  - Leverages FDA resources and expertise
  - Sovereign decision making by each Project Orbis Partner (POP)

Project Orbis Types

Type A

Real time collaboration

- Concurrent submission to participating regulators (within 1 to 2 months)
- FDA and TGA reviewing medicine at same stage of life cycle
- Concurrent review and sharing of Assessment Aid
- Near simultaneous regulatory action
- TGA timeframes generally reduced

Type B

Modified Orbis

- Delays > 3 months
- Overlapping review period and sharing of Assessment Aid
- FDA available to discuss regulatory action
- TGA timeframes may be reduced

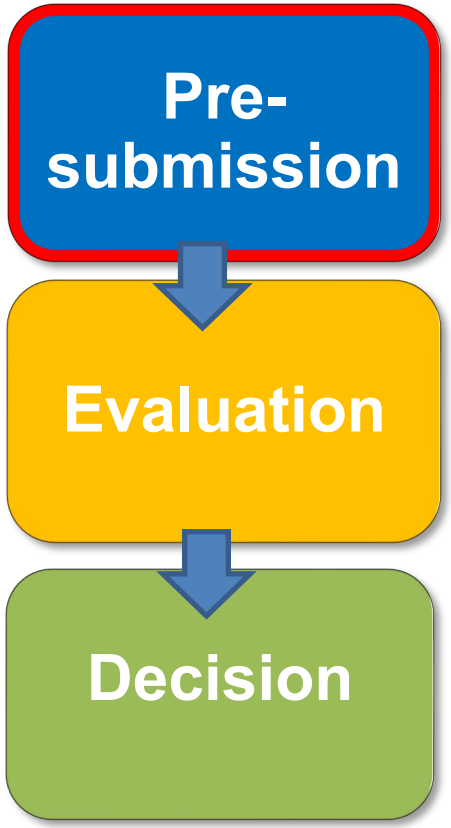
Type C

Written reports only

- FDA has already taken regulatory action (< 1 year)
- FDA makes reports available to POPs
- Interactions during review process may be limited
- TGA timeframes sometimes reduced

Allow for collaboration without concurrent review

Project Orbis process



- Application identification and selection:
  - FDA or US sponsor can propose an application
  - FDA is the primary coordinator for identification of applications
- Agreement of POPs to participate
  - POPs can decline participation (sponsors can still file independently in each jurisdiction)

"Kickoff" meeting to discuss application logistics

Project Orbis process (type A and B)

- POPs conduct their own review and work directly with local applicant
- POPs share Information Requests
  - responses to be sent back to all POPs – reduces duplication
- Collaborative teleconferences with POPs throughout the review (Type A and B only)
  - Internal FDA meetings
  - Discuss various sections of the Assessment Aid
  - Labelling (Product Information)

Project Orbis process

Pre-submission

Evaluation

Decision

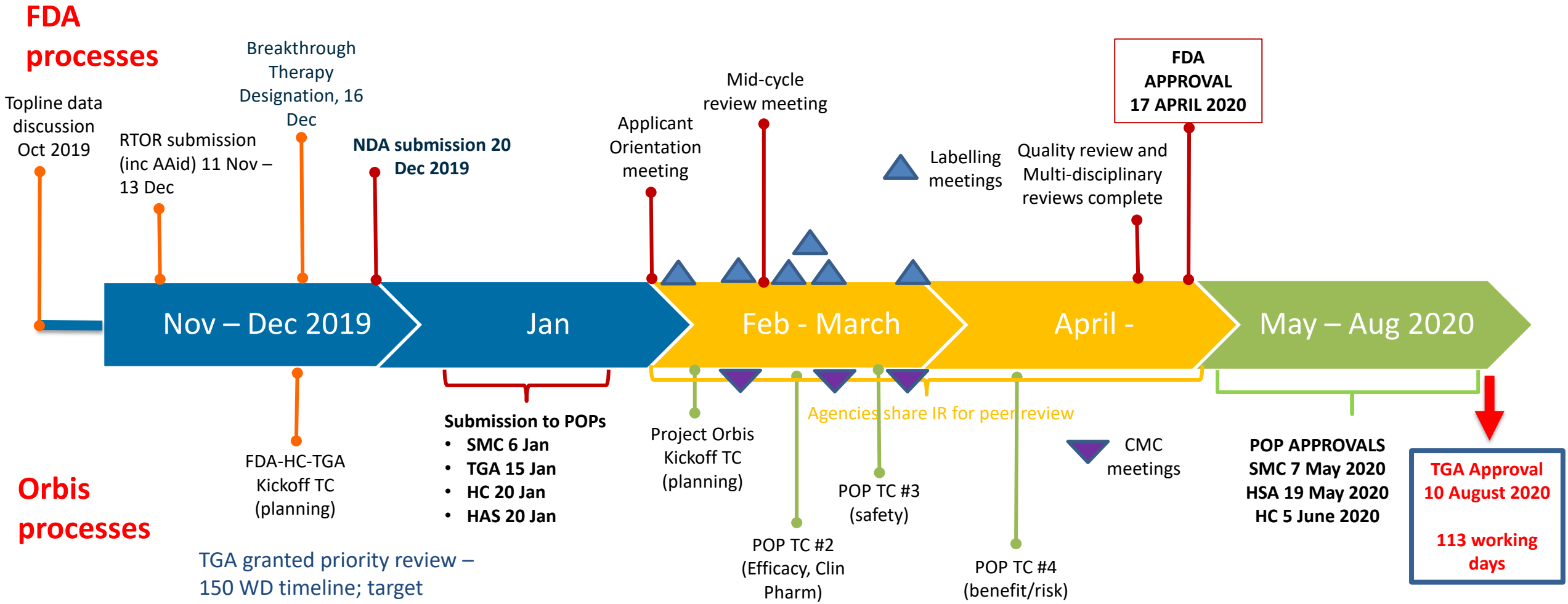
- Independent decision-making by each jurisdiction

- **TGA decision phase includes:**
  - expert advice
  - wording of indications
  - finalisation of product label
  - AusPAR

- Timing of decision not directly linked to FDA decision

After FDA action, FDA is available for major application-related issues noted by POPs up to 6 months after regulatory action

Case study: Tucatinib for HER2+ BC (Type A Orbis)



TGA granted priority review – 150 WD timeline; target decision date: 6 October, 2020

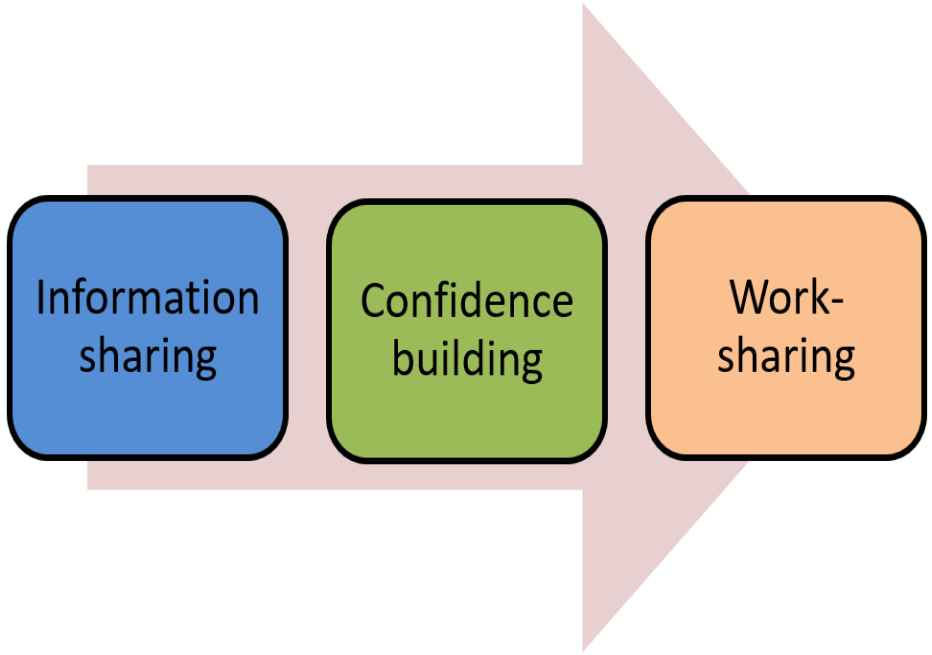
Access New Active Substance (NAS) Work Sharing Initiative

ACCESS CONSORTIUM
AUSTRALIA
CANADA
SINGAPORE
SWITZERLAND
UNITED KINGDOM

- The Australia-Canada-Singapore-Switzerland-UK (Access) Consortium is a group of like-minded, medium sized regulatory authorities.

- Since 2007, Access partners have been collaborating on:
  - generic medicines registration
  - new active substances registration
  - post-market medicine safety
  - development of technical guidelines.

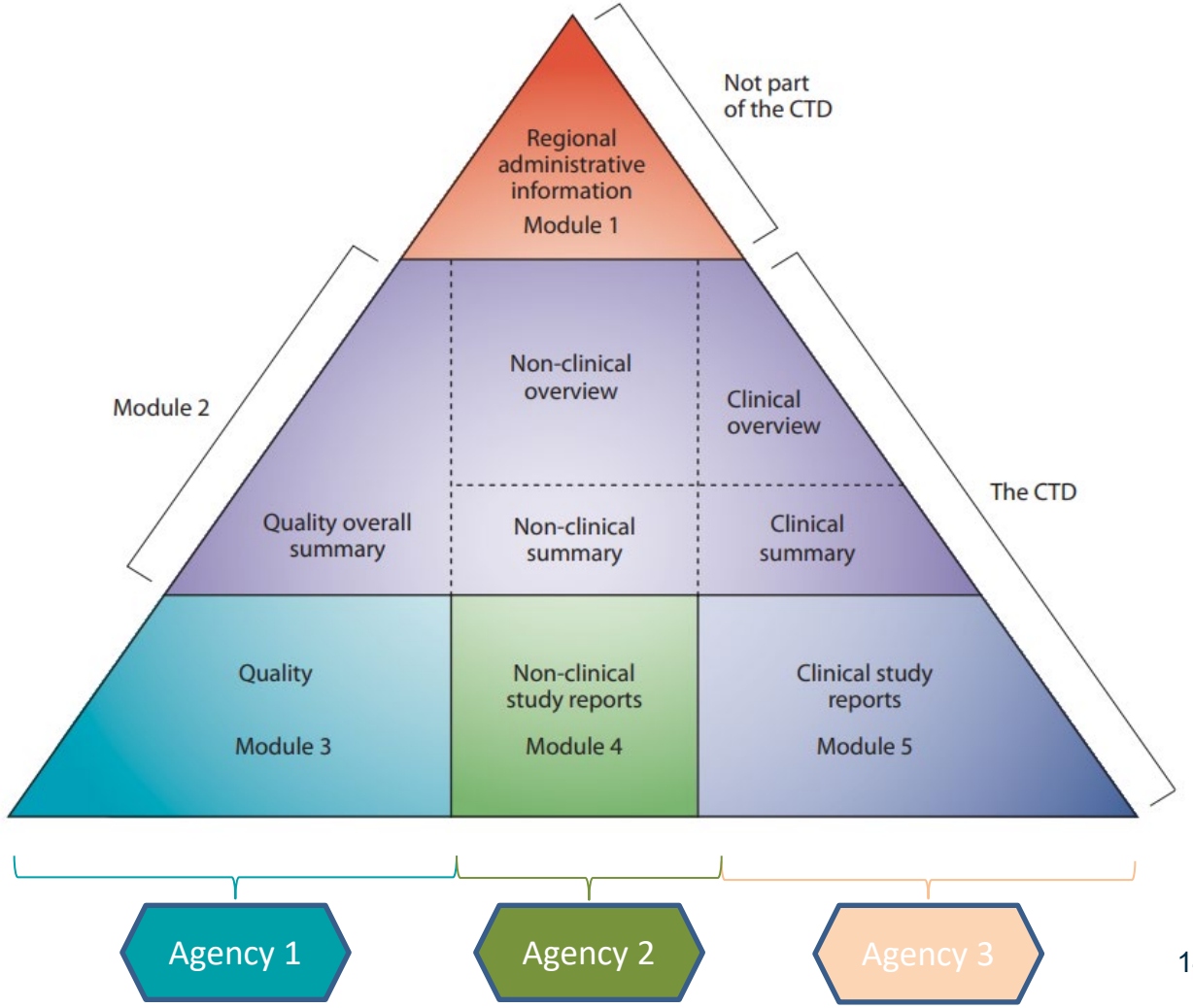
Journey to international work-sharing…..



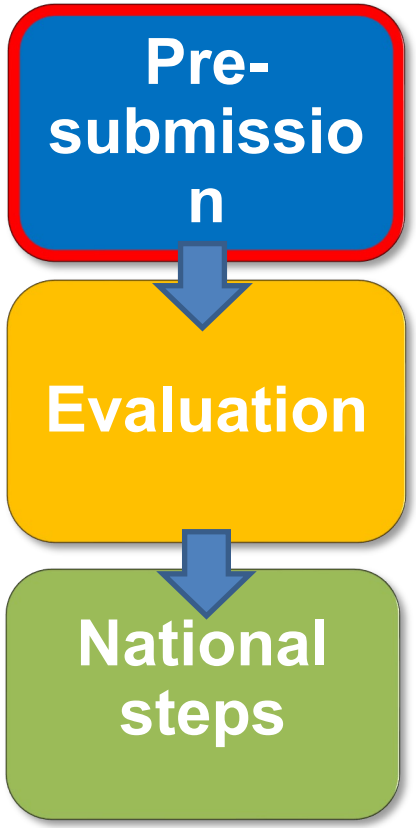
Access New Active Substances Work-sharing Initiative

- Global collaborative review program for drug applications
  - new drugs (new active substances)
  - new indications

- Key features:
  - Divided/shared review of the dossier
  - Information sharing via bilateral confidentiality agreements and Memoranda of Understanding
  - Sovereign decision-making



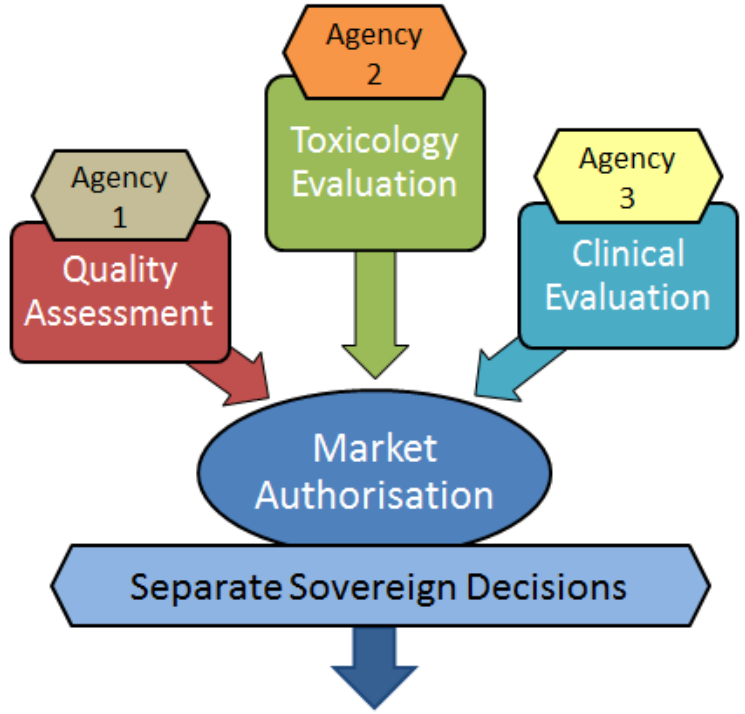
Access work-sharing process



- Applicant Expression of Interest (EOI) *at least **3 months*** before the intended filing date.
- Agreement of partner regulators to participate
- Participating regulators negotiate a division of labour, e.g.:
  - Mod 3 – Quality
  - Mod 4 – Non-clinical
  - Mod 5 – Clinical
- Evaluation plan tailored to each submission through negotiation:
  - Similar to TGA Milestone system
  - Includes time for agency peer review

Access work-sharing process

- Agencies evaluate their assigned module(s) and any country specific aspects:
  - Mod 1 (labels, GMP, RMP)
  - Mod 3 (TGOs, stability, container)
  - Mod 4 (pregnancy category)
  - Wording of indications
- Consolidated technical questions
- Inter-agency interactions throughout the review (evaluator t/c)



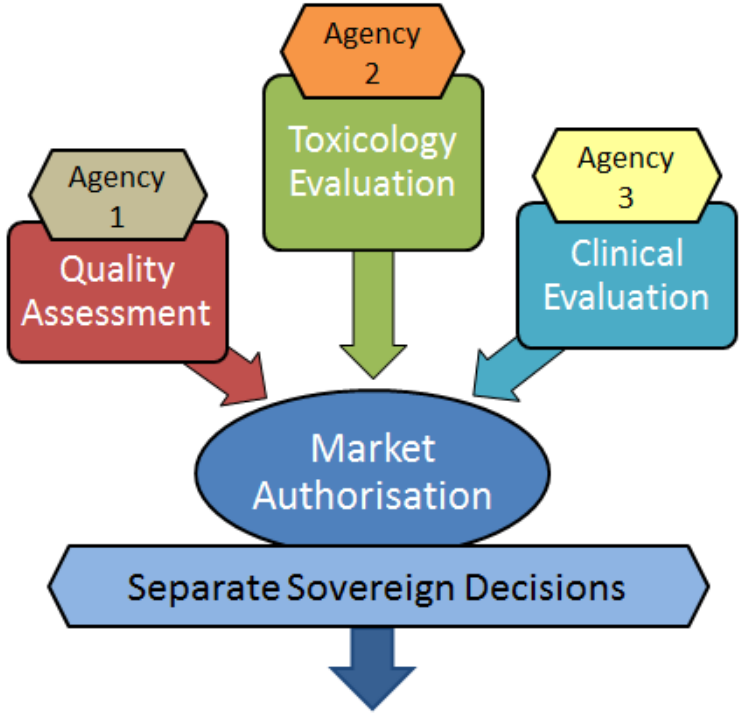
Access work-sharing process

Pre-submission

Evaluation

National steps

- Work-sharing concludes at the end of the evaluation
- **National steps include:**
  - expert advice
  - wording of indications
  - Finalisation of product label
  - subsidy/reimbursement
- Independent decision-making by each jurisdiction
- **Near** simultaneous decisions BUT reimbursement is not part of work-sharing.



Benefits of ACCESS and Project ORBIS

- Opportunity to collaborate, share ideas, consider alternative approaches,
- Exposure to emerging trends, innovations, and learnings
- Encourages earlier submissions to Australia, and encourages submissions that might otherwise not reach Australia
- Faster market access for new products
- Reduced duplication for sponsors
- Improved efficiency with potential to reduce regulatory effort

Challenges with ACCESS and Project ORBIS

- Resource implications for both the coordination and evaluation aspects
- Different national requirements including legislative requirements & different sovereign decisions
- Different processes – timelines; process of communication with sponsors; transparency
- Different submission content or type of submission (Project Orbis)
- Access and Orbis operating as a “pilot”
- We are in a very different time zone

Comparable overseas regulator pathway

TGA uses assessments from Comparable Overseas Regulators (CORs)

- Key features:
  - TGA will accept reports from EMA, MHRA (UK), PMDA (Japan), Health Canada, SwissMedic, US FDA, Health Science Authority (Singapore) (CORs)
  - transparent criteria and guidance for identifying CORs
  - a process for using overseas reports
  - reduces data evaluation
  - retains sovereign decision making

COR report-based process

Requirement	COR-A	COR-B
Time from COR approval to TGA submission	< 1 year	Not specifically time-limited; submission can include completed studies
Registration by COR	Full	Full
Made from human blood or plasma	No	Additional data required but may be eligible
Current GMP licencing	Yes	No, but will need to have submitted prior to application
Stability in Australian climactic zones	Yes	No, will need additional data
Must be full registration by COR; complete unredacted evaluation reports and associated documents in English; application not delayed, deferred, rejected, refused or withdrawn; equivalent indication to the COR		

Comparison of reliance/collaboration pathways

COR Report-based

- Submitting to TGA (only)
- Suitable for **all** therapeutic areas
- Applicants **must** provide reports to TGA that meet legislated criteria
- TGA conducts **abridged assessment** based on COR report(s) in lieu of *de novo* evaluation
- Reduced timeframes (legislated)

Access work-sharing

- Submitting to 2 or more Access members
- Suitable for **all** therapeutic areas
- Standard and priority pathways
- Applicant(s) submit Expression of Interest
- Regulators **divide review of safety quality, efficacy modules**
- Standard timeframes apply

Project Orbis

- Submitting to US FDA **and** TGA (& others)
- Oncology drugs **only**
- Priority, provisional and standard applications
- Suitable applications identified by FDA
- Regulators conduct **parallel, collaborative evaluation** and share information
- Timeframes **may** be reduced

Australian Government

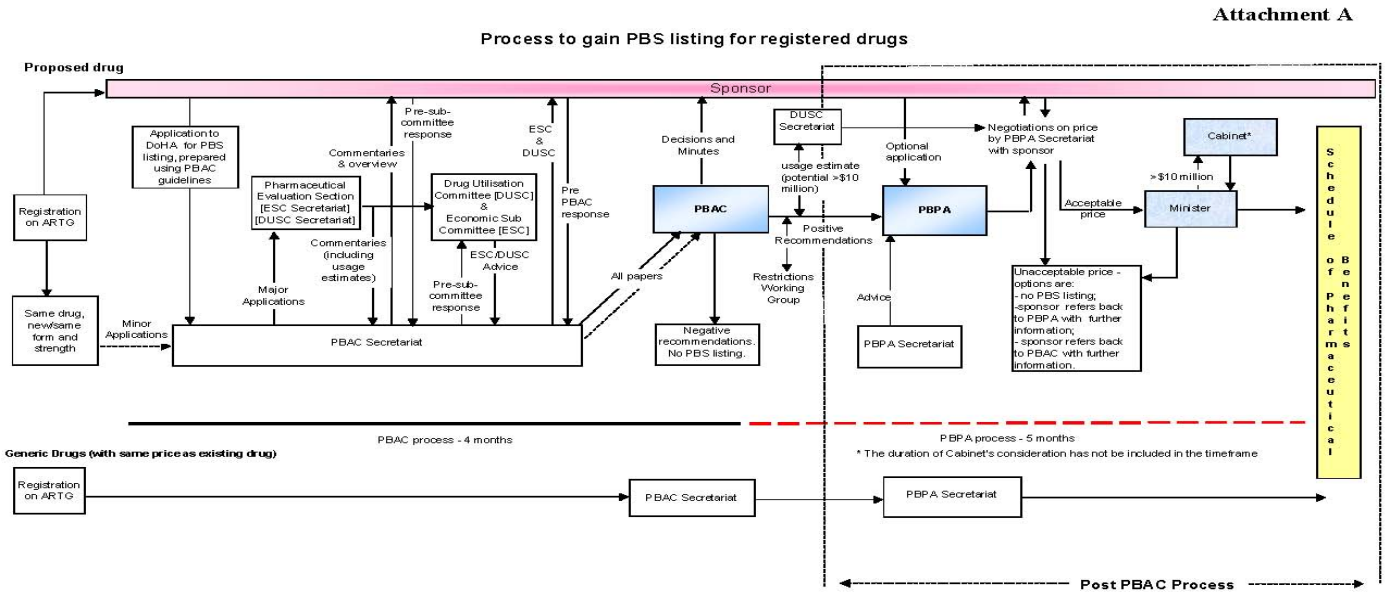
Department of Health

Therapeutic Goods Administration

Back up Slides

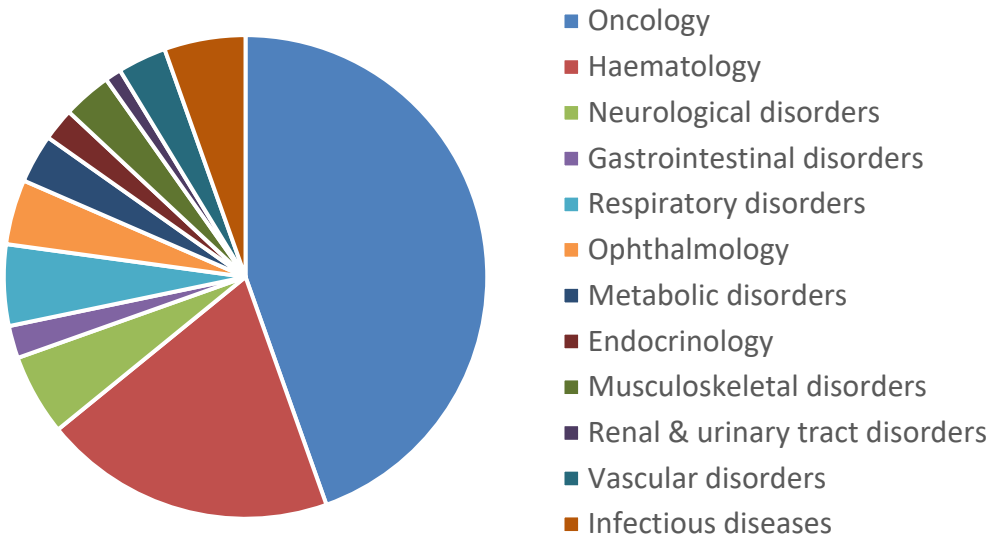
Access to medicines includes subsidy

Process to gain Pharmaceutical Benefits Scheme listing for registered medicines



Designations/determinations: therapeutic area

Approved priority determinations



Approved provisional determinations