Center for Regulatory Excellence

Dr. Max Wegner

SVP & Head,
Regulatory Affairs, Bayer

July 21st , 2021

Bayer Regulatory Affairs and Open Innovation initiated Center for Regulatory Excellence jointly with MassBio

Center for Regulatory Excellence

Provide an efficient path forward for innovation to reach patients

Think-tank sessions

- // Educational sessions on emerging regulatory topics
- // Discuss key challenges that can help provide a path forward for novel modalities/digital health
- // Global regulatory insights
- // Sessions open to all start-ups/biotechs/pharma
- // Format: lecture-based with Bayer colleagues sharing insights into specific topics

Mentorships

- // Provide Insights into Regulatory Activities to “MassCONNECT” companies
- // Bayer regulatory experts share expert knowledge, recommendations and insights for MassCONNECT start-ups into the critical aspects and the most efficient path for a drug or a medicinal product to reach the patients

Chitkala Kalidas

VP & Global Head of
Regulatory Affairs for Oncology
& in vitro diagnostics, Bayer

Navigating FDA's Oncology Center of Excellence and Key Regulatory Considerations for Oncology Drug Development.

Agenda

Topic	Presenter
/// Welcome	Max Wegner
/// Introduction to Oncology at Bayer	Chitkala Kalidas
/// Oncology at FDA	Scott Greenfeder
/// Overview of FDA interaction opportunities	Nana Hagan
/// Overview of IVD/CDx development and regulatory	David Donne
/// Q&A	Moderator: Todd Paporello
/// Closing Remarks	Max Wegner

Introduction to Oncology at Bayer

Chitkala Kalidas

Bayer AG

- **Headquarter: Leverkusen, Germany**
- **Employees** 99,500
- **Full year sales** 41 billion Euro
- **Subsidiaries** 240
- **R&D investment** 7.1 billion Euro

Status: 31 December 2020; Source: www.investor.bayer.com

Bayer Oncology Operating Model
Oncology Strategic Business Unit

- Objectives of the Business Unit
  - Strategically manage and deliver upon the Oncology portfolio with a more focused and integrated approach in a rapidly evolving environment
  - Accelerate the development and delivery of our medicines to patients
  - Foster a cross-functional Oncology focus and One Oncology Mindset

Key Focus Areas

1. Oncogenic Signaling
2. Targeted Alpha Therapies
3. Immuno-Oncology & Cell Therapy

Bayer Oncology Approved Products

Six marketed products in the US

Product	Indication(s)
ALIQOPA™ (copanlisib)	Relapsed FL
NEXAVAR™ (sorafenib)	HCC, RCC, Thyroid Cancer
NUBEQA™ (darolutamide)	nmCRPC
STIVARGA™ (regorafenib)	mCRC, HCC, GIST
VITRAKVI™ (Larotrectinib)	Solid tumors w/ NTRK gene fusion
XOFIGO™ (radium Ra 223 diCl)	Bone mCRPC

Bayer Oncology Pipeline
Selected programs under development

Product	MOA	Collaboration/Internal
BAY 2416964	AhR inhibitor (Immuno-Oncology platform)	Collaboration w/ German Cancer Res Ctr
BAY 2666605	SLFN12-PDE3A complex inducer (Oncogenic Signaling platform)	Collaboration w/ Broad Institute
Elimusertib (BAY 1895344)	ATR inhibitor (Oncogenic signaling platform)	Internal
Bapotulimab (BAY 1905254)	ILDR2 Ab (IO platform)	Internal
BAY 2315497	PSMA thorium conjugate (Targeted Alpha Therapies platform)	Internal
BAY 2701439	HER2 thorium conjugate (TAT platform)	Internal

Presenters:

Scott Greenfeder

VP & Group Head of
Oncology Regulatory
Strategy Group 2, Bayer

Nana Hagan

VP & Group Head of
Oncology Regulatory
Strategy Group 1, Bayer

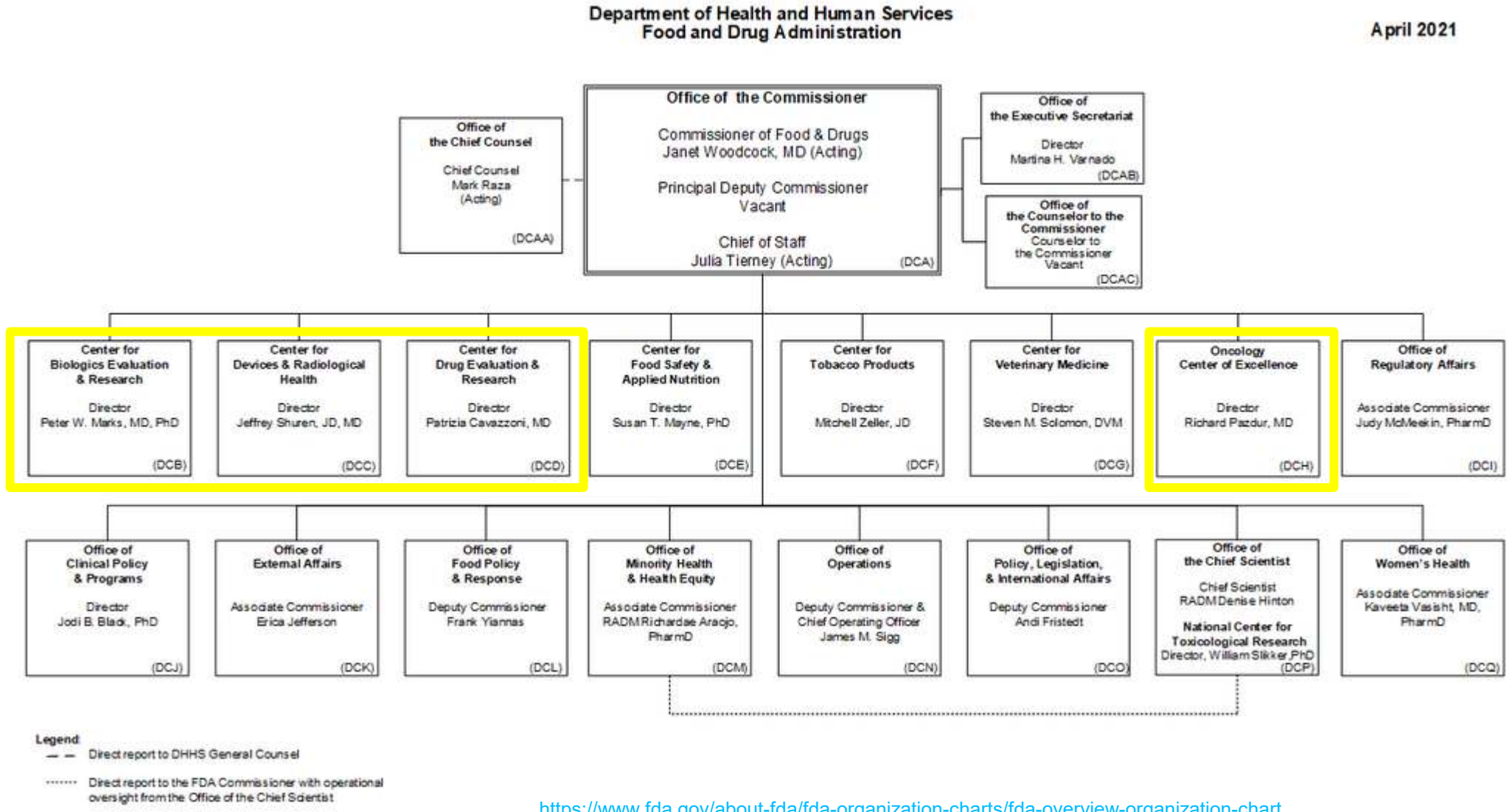
David Donne

VP & Group Head of
Oncology Regulatory
Strategy Group 3, Bayer

Oncology at FDA

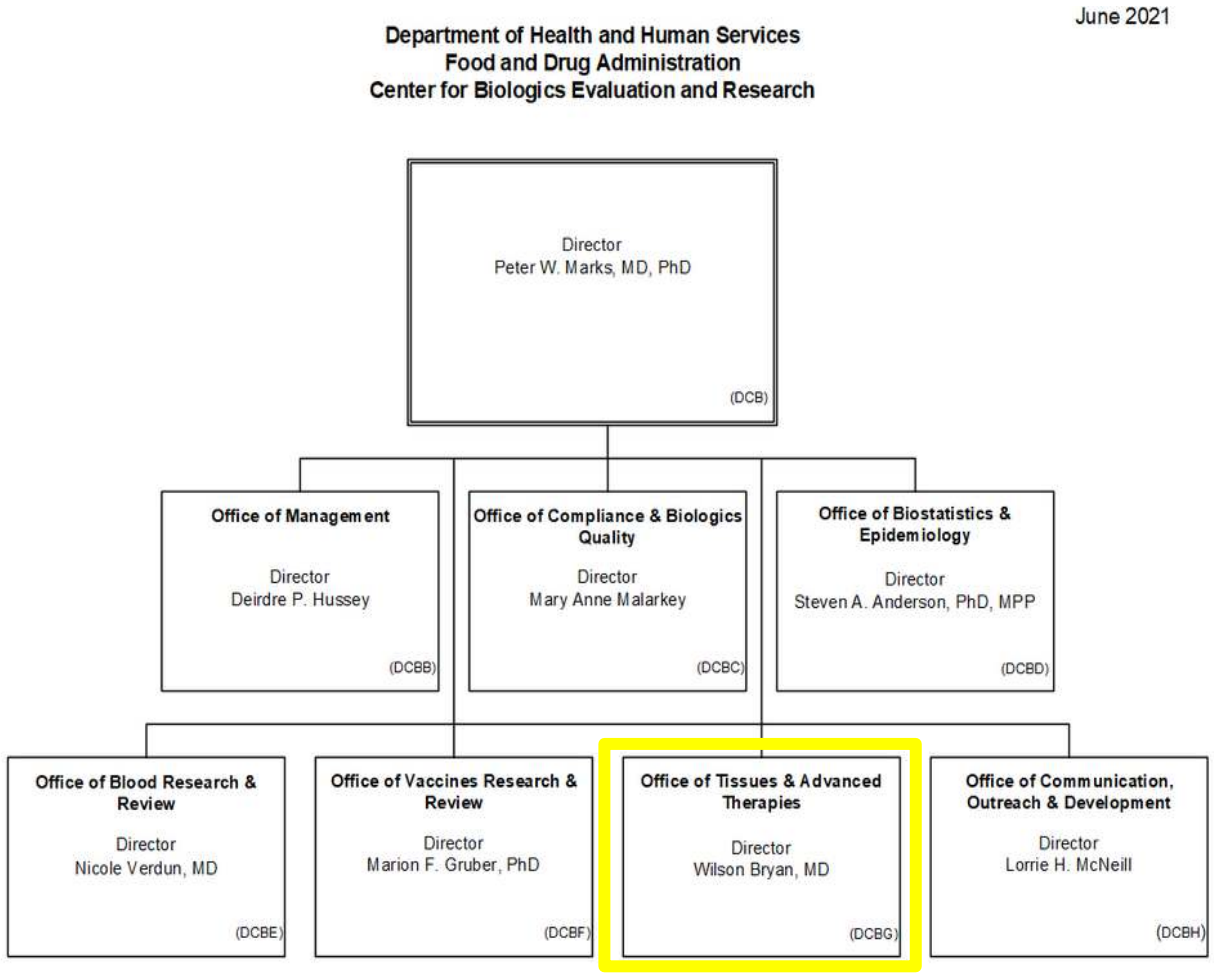
Scott Greenfeder

FDA Organization

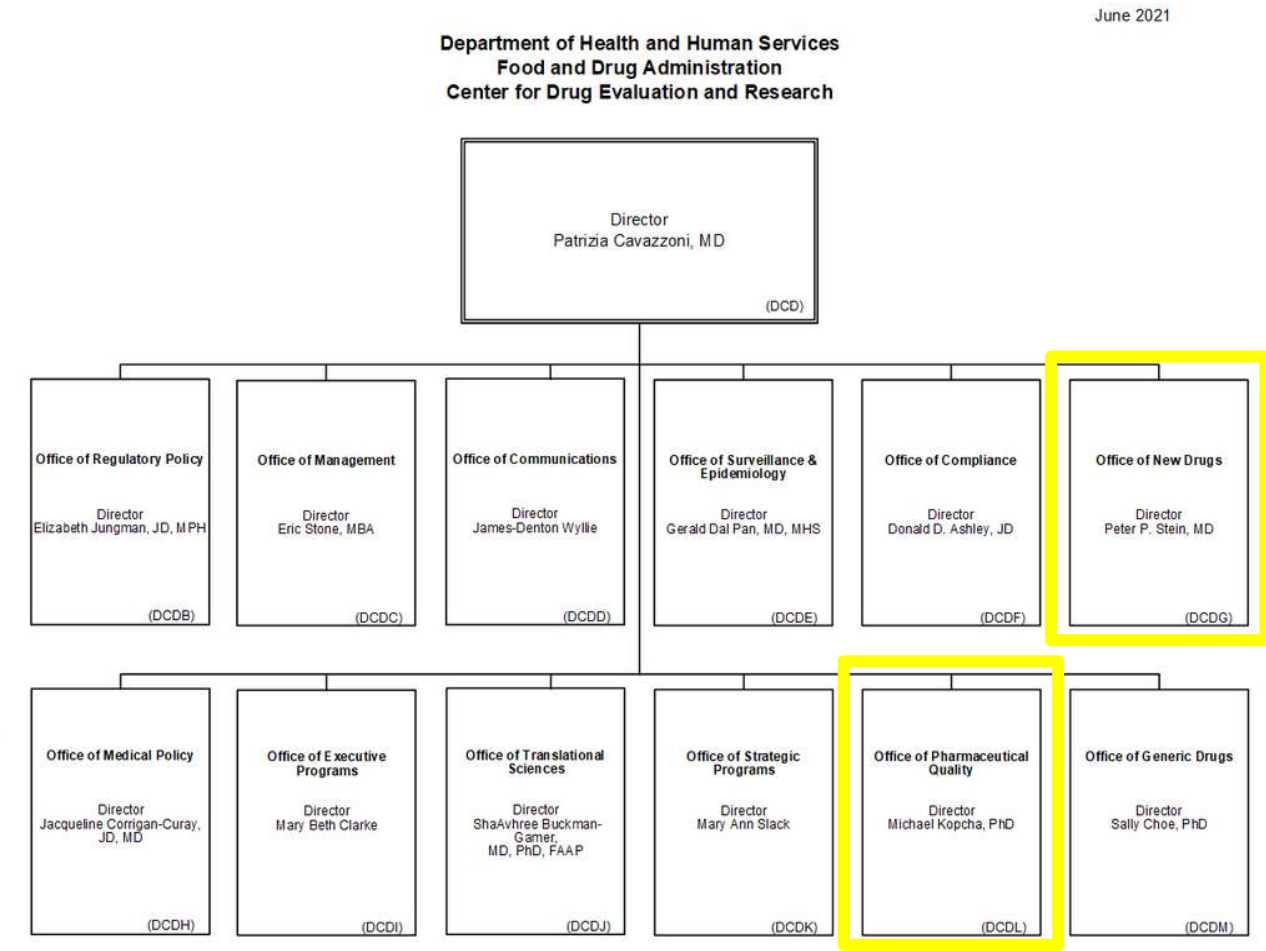


https://www.fda.gov/about-fda/fda-organization-charts/fda-overview-organization-chart

FDA Organization

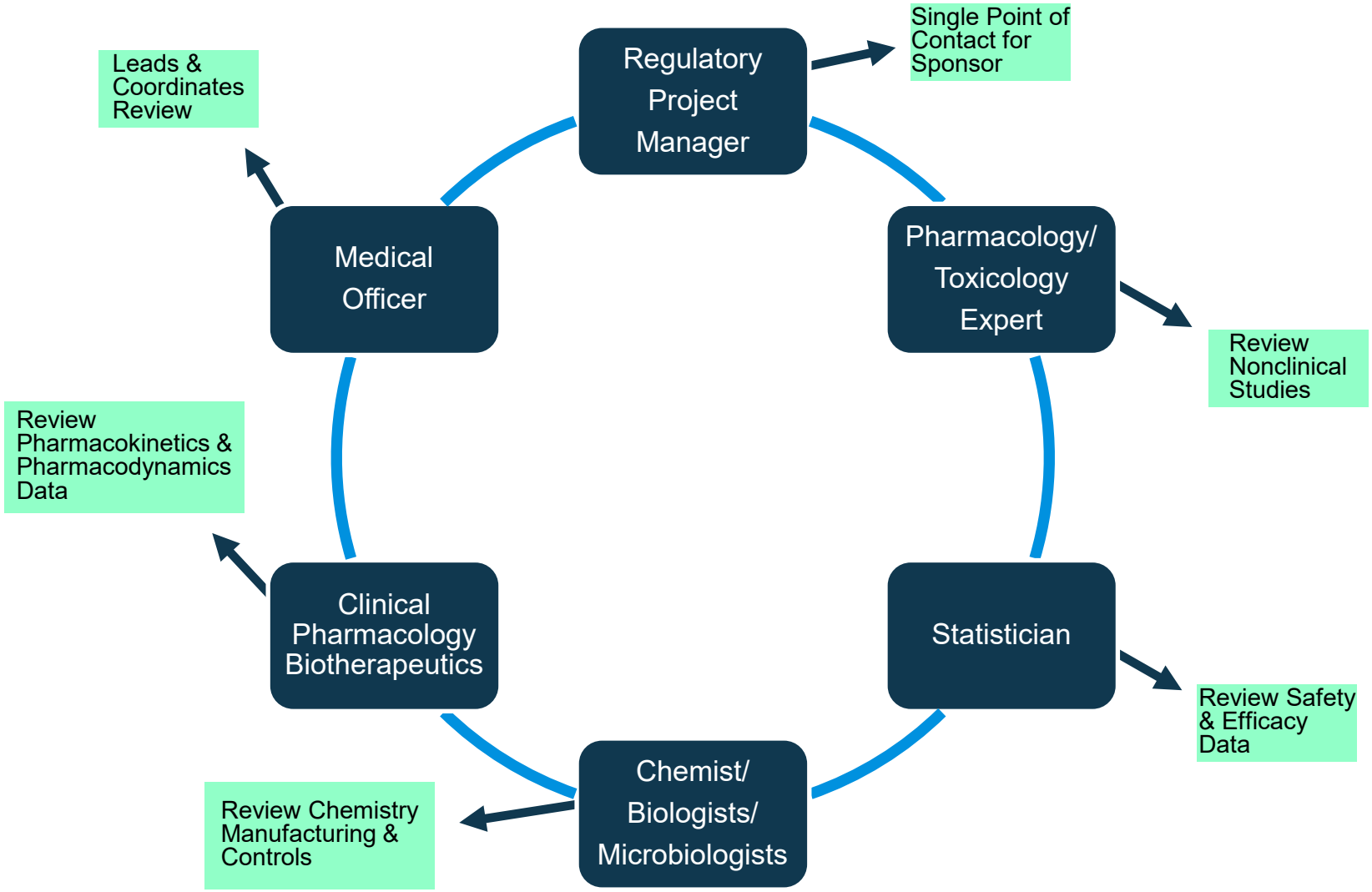


CBER Organization



CDER Organization

FDA Interdisciplinary Review Teams



FDA Office of New Drugs (OND)

OCHEN	• Cardiology, Hematology, Endocrinology and Nephrology
OII	• Immunology and Inflammation
ORPURM	• Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
OID	• Infectious Diseases
ON	• Neurosciences
ONPD	• Nonprescription Drugs
OOD	• Oncologic Diseases
OSM	• Specialty Medicine (Imaging and Radiation Med/Opthalmology)
OTBB	• Therapeutic Biologics and Biosimilars
COA Staff	• Clinical Outcome Assessments
Labeling Policy Team	• Product Labeling

CDER Offices and Divisions

FDA Office of Oncologic Disease (OOD)

DO1	• Breast, Gynecologic & Genitourinary cancers, cancer supportive care
DO2	• Thoracic Head & Neck, Neuro-oncology, Rare cancers, Pediatric solid tumors
DO3	• Gastrointestinal, Superficial cutaneous cancers, melanoma, sarcoma
DHM1	• Acute Leukemia and Myelodysplasia, Chronic Myeloid Leukemia and others
DHM2	• Lymphoma, Chronic Lymphocytic Leukemia, Multiple Myeloma, and other plasma cell malignancies
DHOT	• Nonclinical Review Division for Oncology products

OOD Review Divisions

DO = Division of Oncology
DHM = Division of Hematologic Malignancies
DHOT = Division of Hematology Oncology Toxicology

FDA Oncology Center of Excellence (OCE)

Vision

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

Mission

…to achieve patient-centered regulatory decision-making through innovation and collaboration.

OCE works with FDA Divisions for products selected for expedited programs to:

- Provide a unified clinical review to promote development of safe and effective oncology products
- Build on cross-center collaboration by providing input to selected INDs that are under expedited program
- Implement common decision-making standards for Breakthrough Therapy and Fast Track designation for all oncology therapeutic products

OCE Website

FDA OCE Key Programs

For Patients and the Public

- FDA Resources for Patients
- Patient Friendly Language for Cancer Clinical Trials
- Project Patient Voice
- Pediatric Oncology Program

For Product Sponsors

- Assessment Aid
- Real Time Oncology Review (RTOR)
- Project Orbis

OCE Website

New Pediatric Legislation: FDARA 504

RACE ("Research to Accelerate Cures and Equity for Children" Act

- FDARA section 504 = amends "PREA" (Pediatric Research Equity Act)
- Applies exclusively to NMEs "intended for the treatment of an adult cancer"
- Required pediatric studies based on molecular target not adult indication
- Introduces lists of relevant and non-relevant molecular targets
- Broadens options for granting waivers and deferrals (postponement) for required pediatric studies
- Orphan drugs DO NOT receive an automatic waiver
- Fulfilment not associated special incentives to Sponsors
- Purpose of legislation is to accelerate the timeline of early phase studies, not to increase the number

OCE Website

Overview of FDA interactions, expedited development opportunities and special designations

Nana Hagan

Types of Advice that are Appropriate for Sponsors to Seek

Clinical topics during drug development

Clinical/Statistics	Safety	Clinical Pharmacology
• Trial design, e.g. population, size, comparator • Validity of outcomes and endpoint	• Safety issues • Size of safety database • Concern with specific populations • PV plans • Risk evaluation and mitigation strategies	• Dose selection and population • Use in specific populations • Drug-drug interactions

https://www.fda.gov/files/drugs/published/Best-Practices-for-Communication-Between-IND-Sponsors-and-FDA-During-Drug-Development.pdf

Types of Advice that are Appropriate for Sponsors to Seek

Nonclinical and CMC topics during drug development

Nonclinical pharmacology	Toxicology	Product quality/CMC
• Mechanism of action	• Genetic toxicology • Reproductive and developmental toxicology • carcinogenicity	• Comparability of clinical and commercial lots • Shelf life and stability • Characterization of drug product/substance

https://www.fda.gov/files/drugs/published/Best-Practices-for-Communication-Between-IND-Sponsors-and-FDA-During-Drug-Development.pdf

Types of Advice that are Appropriate for Sponsors to Seek

Pediatric and regulatory topics during drug development

Pediatric

- Proposed pediatric development plan
- Pediatric dosing

Regulatory

- Expedited programs
- Defer or waive studies

https://www.fda.gov/files/drugs/published/Best-Practices-for-Communication-Between-IND-Sponsors-and-FDA-During-Drug-Development.pdf

Types of Formal Meetings Between FDA and Sponsors

Type	A	B	B (EOP)	C

Description	• Meetings to help a stalled program
	  • dispute resolution
	  • clinical holds
	  • SPA
		• Meeting before major submission
		  • pre-IND
		  • pre-NDA/BLA
		• Meetings to discuss programs with breakthrough therapy designation
			• Meeting held at end of a clinical phase of development
			  • EOP1
			  • EOP2/pre-Ph3
				• Meetings that fall outside Type A and Type B topics
				  • general guidance
				  • consultation on the use of new surrogate endpoints*)

Response time	14 days	21 days	14 days	21 days
Scheduling - F2F/VC/TC/WRO (after receipt of request)	30 days	60 days	70 days	75 days
FDA receipt of briefing package	With meeting request	30 days before meeting/WRO	50 days before meeting/WRO	47 days before meeting/WRO
FDA's comments to sponsor	No later than 2 days before meeting		No later than 5 days before meeting	
FDA meeting minutes	Within 30 days after meeting			

SPA – special protocol assessment, EOP-End of phase, F2F – face to face meeting, TC – teleconference, WRO – written response only

* Meeting package is due at time of meeting request

https://www.fda.gov/media/109951/download

Additional Opportunities for Interaction with FDA

Type	F	INTERACT

Description	• Pediatric Oncology Product Development Early Advice Meeting[1]
	• Advice on the development of iPSP
		• Informal meeting on innovative investigational products that introduce unique challenges and issues[2]
		  • General guidance
		  • Issues critical to early development not yet at the pre-IND meeting phase

Response time	Contact review division	21 days
Scheduling time - TC (after receipt of meeting request)		90 days
Scheduling time - WRO (after receipt of WRO request)		Not applicable
FDA receipt of briefing package		With meeting request
FDA comments to sponsor		No later than 1 day before meeting
FDA meeting minutes		Not applicable

INTERACT – INitial Targeted Engagement for Regulatory Advice on CBER producTs

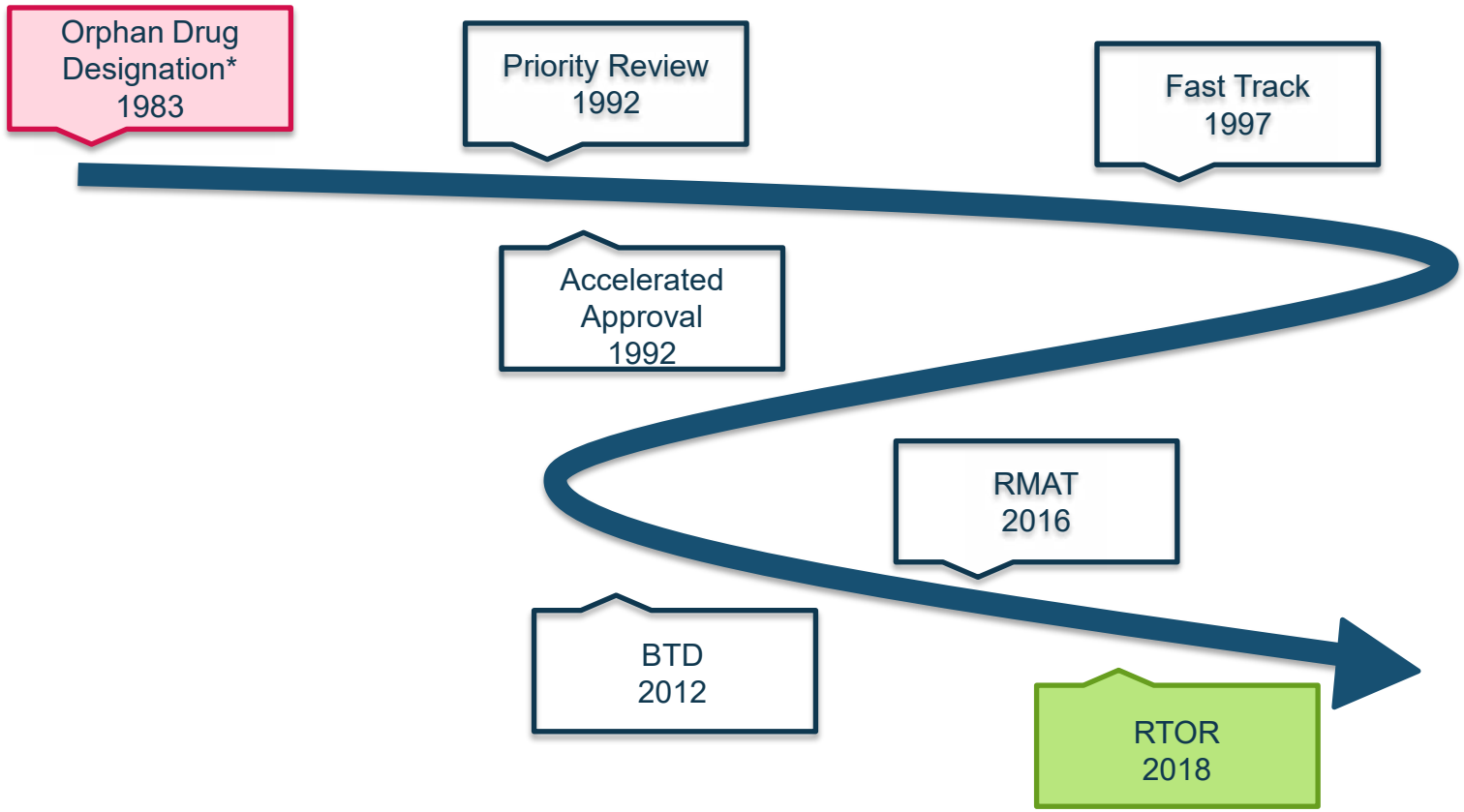
1. https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology-product-development-early-advice-meeting-type-f1
2. https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings

Best Practices for FDA Meetings

Planning	Rehearsal	Conduct	Debrief	Implementation
Consider timelines	Team roles and responsibilities	Arrive early	Review and align on meeting points ASAP	Follow up on FDA requests
What's the meeting objective? (questions, position, participant)	Fall back positions	Facilitate meeting/ Stick to the agenda	Draft minutes and Communicate to stakeholders	Apply FDA advice
Consider meeting format (TC, F2F, written feedback)	FDA preliminary comments	Manage time well	Review FDA minutes	Inform FDA of changes or delays
Quality briefing book and meeting request	Mock meeting	Take notes Ensure mutual understanding		

FDA Expedited Programs and Orphan Drug Designation

FDA Expedited Programs and Orphan Drug Designation



Goals of Expedited Programs

- ✓ Priority review, accelerated approval, fast track, BTD, and RMAT are expedited development programs. RTOR is an expedited review program.
- ✓ Intended to help ensure that therapies for these conditions are approved and available to patients as early as it can be concluded that the therapies' benefits justify their risks
- ✓ Allow for earlier attention to drugs that have promise in treating such conditions

* Orphan drug designation qualifies sponsors for certain benefits but does not mean an expedited path

BTD – breakthrough therapy designation; RMAT – Regenerative Medicine Advanced Therapy; RTOR – Real Time Oncology Review

Requirements for FDA's Expedited Programs

	Priority Review	Accelerated Approval	Fast-Track	BTD	RMAT	RTOR
Year issued, enacted or piloted	1992	1992	1997	2012	2016	2018
Regenerative medicine therapy					✗	
Potential to fill unmet medical need based on clinical or nonclinical data			✗			
Intended for serious condition	✗	✗	✗	✗	✗	
Potential for significant improvement: safety/efficacy	✗	✗				
Effect on surrogate endpoint reasonably likely to predict clinical benefit		✗				
Preliminary clinical evidence of substantial improvement over existing therapy				✗		
Preliminary clinical evidence of potential to address unmet medical need					✗	
Substantial improvement over available therapy by evidence from clinical study						✗
Straightforward trial design and easily interpretable endpoints						✗

BTD – breakthrough therapy designation; RMAT – Regenerative Medicine Advanced Therapy; RTOR – Real Time Oncology Review

Considerations for FDA's Expedited Programs

Considerations for Sponsors	Priority Review	Accelerated Approval	Fast-Track	BTD	RMAT	RTOR
When to submit	With NDA/BLA	Discuss during development	With IND or after	With IND* or after		Topline results
Earlier and more frequent communication with FDA			✗	✗	✗	
FDA commitment and intensive guidance on efficient drug development				✗	✗	
Option for rolling NDA/BLA submission			✗	✗	✗	
Early iterative engagement with FDA, allowing for the submission of key data prior to complete NDA/BLA						✗
Potential for shorter review time				✗	✗	✗
Review time shortened to 6 months after submission	✗					
Approval based on effect on surrogate or intermediate endpoint likely to predict clinical benefit		✗				

* Submission would need to include preliminary clinical data

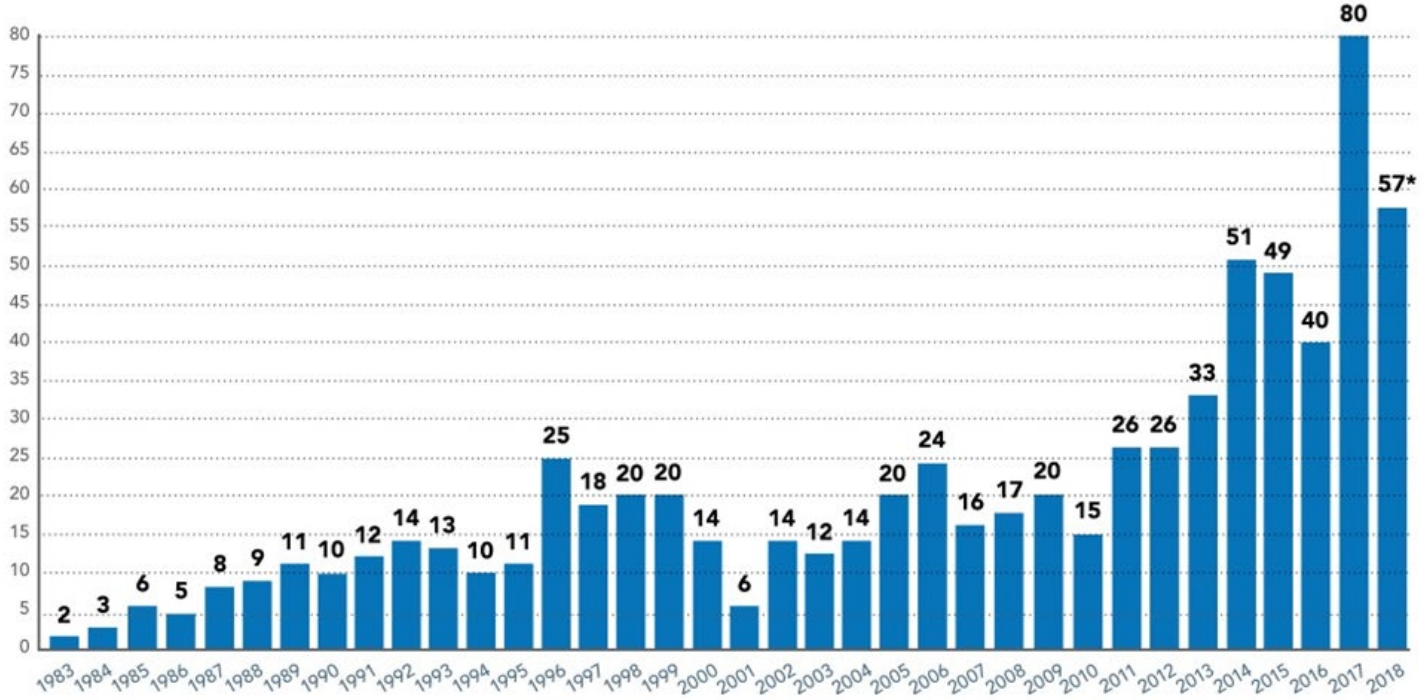
BTD – breakthrough therapy designation; RMAT – Regenerative Medicine Advanced Therapy; RTOR – Real Time Oncology Review

Orphan Drug Designation

Requirements

- The product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition
- Demonstration that the intended condition is rare - affecting **less than 200,000** individuals in the USA
- Evidence of a scientific rationale establishing a medically plausible basis for the use of the product for the rare condition

Approvals of Orphan Drug Designated Products and Incentives



Source: IQVIA; FDA, search orphan drug designations and approvals. 2018 Sep. Available from: www.accesdata.fda.gov/scripts/opdlisting/oopd/

Incentives for Orphan Drug Designation

- ✓ Marketing exclusivity (7 years following approval)
- ✓ Tax credits (for $ invested in clinical development)
- ✓ FDA Grants/Contracts (typically university investigators, small companies)
- ✓ Protocol assistance (written FDA advice on nonclinical/clinical studies)
- ✓ Exemption from NDA/BLA user fees (unless application also includes non-orphan disease/condition)

Orphan drug designation does not mean an expedited development path

Overview of IVD/CDx development and regulatory considerations

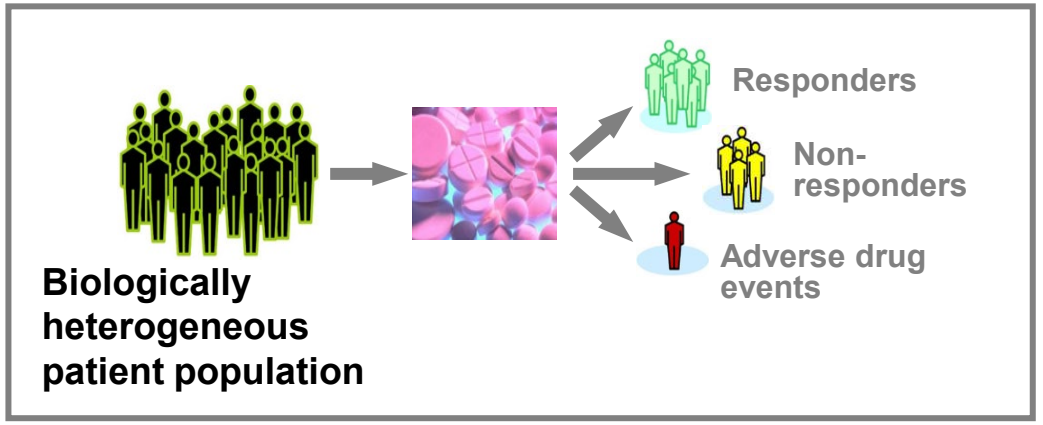
David Donne

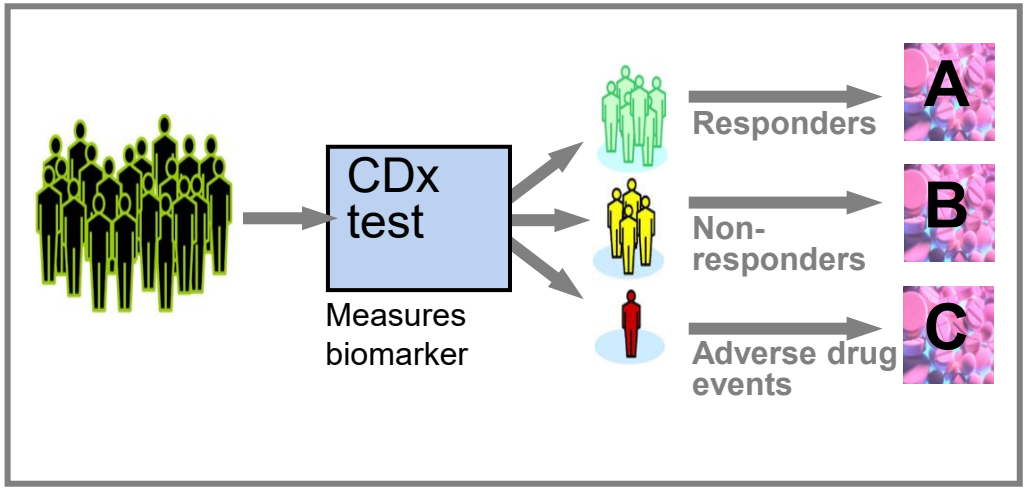
Personalized Oncology and Biomarkers

Trial and error

vs

Informed treatment decision





What Is an In Vitro Diagnostic product (IVD)?

Definition:

In vitro diagnostic products are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3]

What Is a Companion Diagnostic (CDx)?

A companion diagnostic is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product.

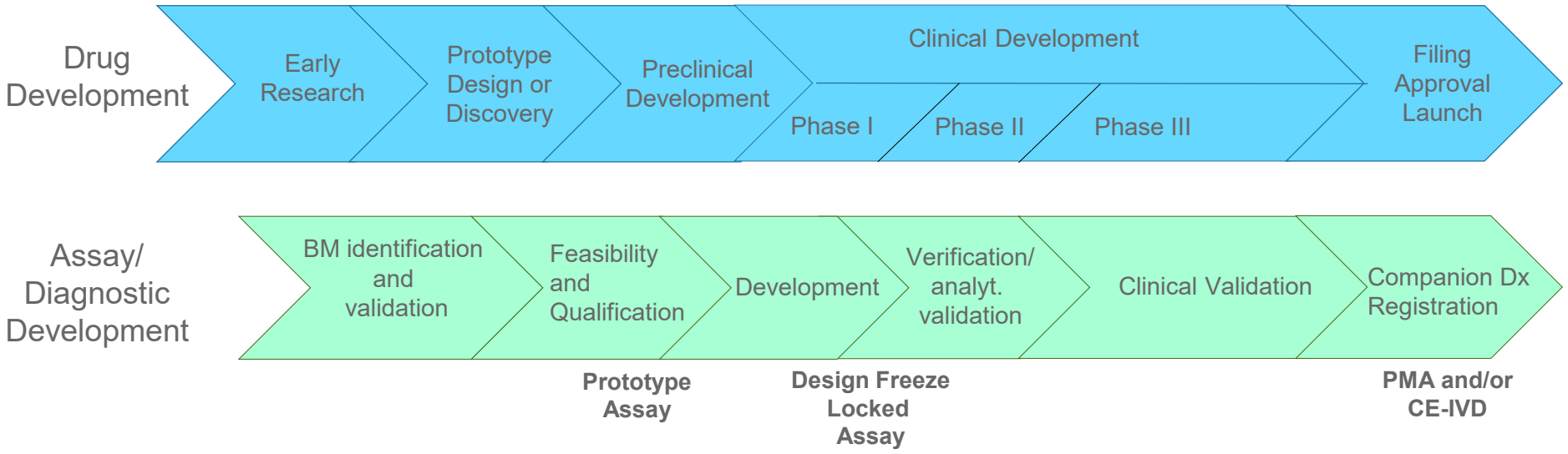
Companion diagnostics can:

- identify patients who are most likely to benefit from a particular therapeutic product;
- identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or
- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

Integrated Drug/Diagnostic Development Model

- Can patients be partitioned by likelihood of drug response based on a diagnostic test?
- Drug response and efficacy/reduced risk (safety) depends on identification of appropriate subpopulation
- Successful path forward will only be as good as the drug and diagnostic device combination
- *“Does the diagnostic hold the drug development/approval hostage?”*

Managing the Complexity of Tx/Dx Co-Development



- If an investigational IVD is utilized in a clinical study, requirements of Investigational Device Exemption (IDE) need to be addressed
- If a CDx is required, a contemporaneous IVD CDx and its corresponding therapeutic product approvals are generally required unless exempted

Key Aspects of Tx/Dx Co-Development

Don’t let Dx development hold drug development/registration hostage

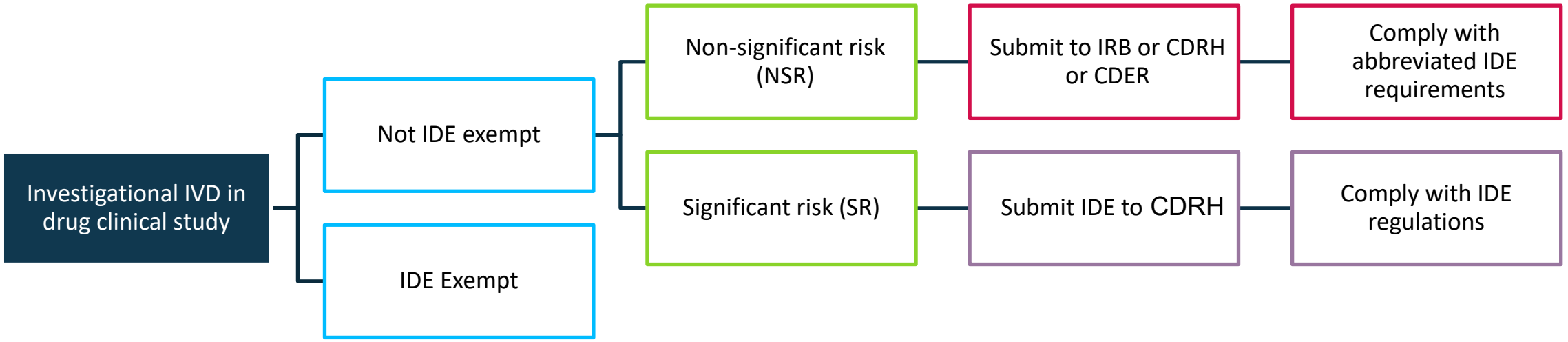
IVD testing as enabler of biomarker driven drug clinical program:

- Selection of an IVD test: IHC, PCR, FISH, NGS
- Selection of IVD partner(s)
- Regulatory clearance for the use of IVD test
  - IDE exempt or IDE non-exempt
  - Study risk determination (SRD)

CDx development as requirement/condition for drug marketing approvals:

- Selection of CDx partner
- Investigational Device Exemption (IDE)
- Pre-Market Application (PMA)

IVD Test in Drug Trials: IDE Exempt ? Significant Risk?

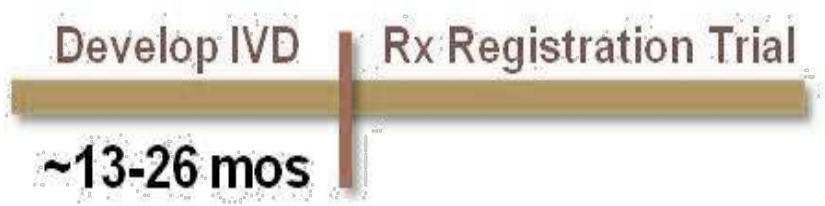


Strategies for Developing a CDx to Enable Tx Registration

Ideal Co-Development:

Prospective Clinical Trial Fully validated IVD CDx Test

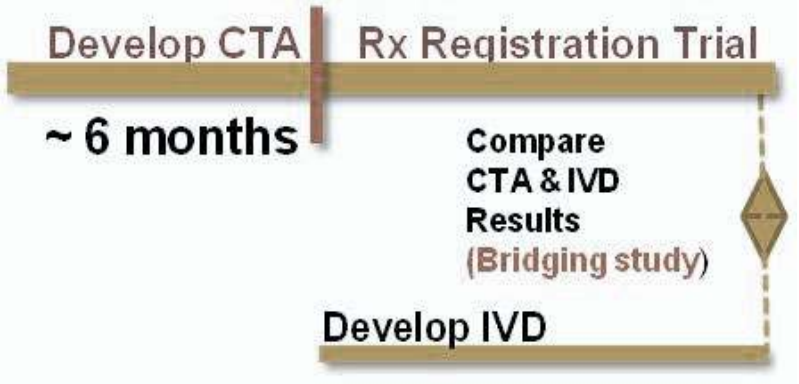
- Preferred approach; allows early partnerships agreements & CDx development initiation
- Biomarker identified early in drug clinical development
- Final CDx in registrational trial
- Clinical validation of the CDx in the pivotal clinical trial



Alternative Option:

Bridging Strategy using CTA followed by IVD CDx

- Biomarker identified later. To enable incorporation in clinical development need a CTA
- Creates additional requirements for clinical study design
  - Retrospective samples, clinical trial assay design, agreement on technology for clinical trial assay and CDx IVD, etc.)
- Risk to the drug (discordance between CTA & IVD). Impact on efficacy analysis



Summary

- A biomarker IVD test can accelerate drug development
- Separate Dx regulatory requirements must be met to enable drug trials/approvals – identify a Dx partner early
- Concurrent approvals of Dx and Tx requirement for full approvals of Tx (unless postponed for accelerated approvals) – don’t let Dx development hold Tx trial/approval hostage

Panelists:

Chitkala Kalidas
VP & Global Head of Regulatory Affairs for Oncology & in vitro diagnostics, Bayer

Max Wegner
SVP & Head,
Regulatory Affairs, Bayer

Scott Greenfeder
VP& Group Head of Oncology Regulatory Strategy Group 2, Bayer

Nana Hagan
VP& Group Head of Oncology Regulatory Strategy Group 1, Bayer

David Donne
VP& Group Head of Oncology Regulatory Strategy Group 3, Bayer

Moderator:

Todd Paporello
VP & Head,
Regulatory Affairs Americas, Bayer

Thank you for joining!

Dr. Max Wegner

SVP & Head,
Regulatory Affairs, Bayer