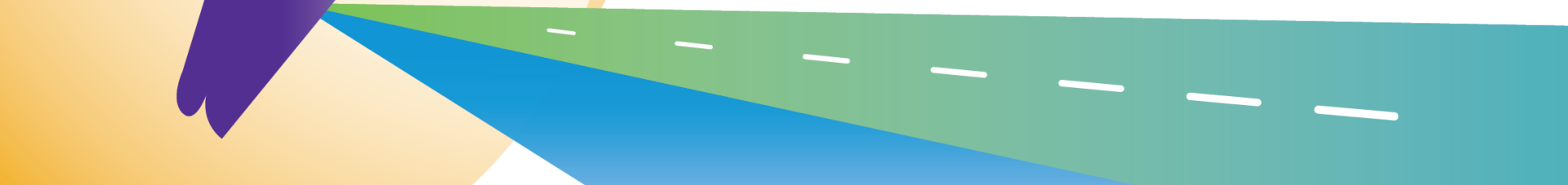
Gulf Coast Consortia
Foundations of Cancer Therapeutics: Commercialization

Navigating NDA Approval and Launch: Keep the End in Mind

Bioscience Research Collaborative
Rice University
August 12-16, 2024



About Presenter

Cheryl Beal Anderson, PharmD MBA
ACE Regulatory Affairs Consulting
Founder & CEO

Qualified by Experience

- Laboratory Technician, microbiology, UTMB Galveston
- Licensed Pharmacist (Texas, Active)
- Academic faculty member, UT (Austin) and UIC Colleges of pharmacy
- Psychiatry Clinical Research Unit, Associate Director
- Pharma/biotech industry regulatory affairs professional (25 + years)
  - Eli Lilly & Co., Lundbeck, LLC, Upsher-Smith Laboratories, LLC
  - Senior Analyst, Manager (CNS), US Regulatory Affairs Strategy Director (CNS, oncology, cardiovascular, autoimmune), Diversity Council, Global Regulatory Director (neurology), Executive Team and SVP/VP Regulatory Affairs, Drug Safety and Quality
  - Pre-clinical, IND, Phase 1-3, EOP2, Pre-NDA, NDA, FDA Advisory Committee, Commercial Launch, On-Market Compliance, REMS, Life-Cycle Management, Product Acquisition, M&A

Qualified by Education and Training

- St. Joseph University (MBA, Healthcare and Pharmaceutical Marketing)
- Executive Business Education (UVA Darden, UM Ross, Simmons Univ Simmons)
- UTA/ UTHSCSA/ TDMHMR (ASHP Accredited Clinical Pharmacy Residency)
- University of Texas at Austin (Doctor of Pharmacy)
- University of Texas at Austin (BS Pharmacy; RPh)
- Texas A&M University (Biomedical Science)

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Agenda

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01

Target Product Profile

02

Key Interactions with Regulatory Health Authorities

03

New Drug Application To Approval

04

Launch and Post Approval

01

Target Product Profile

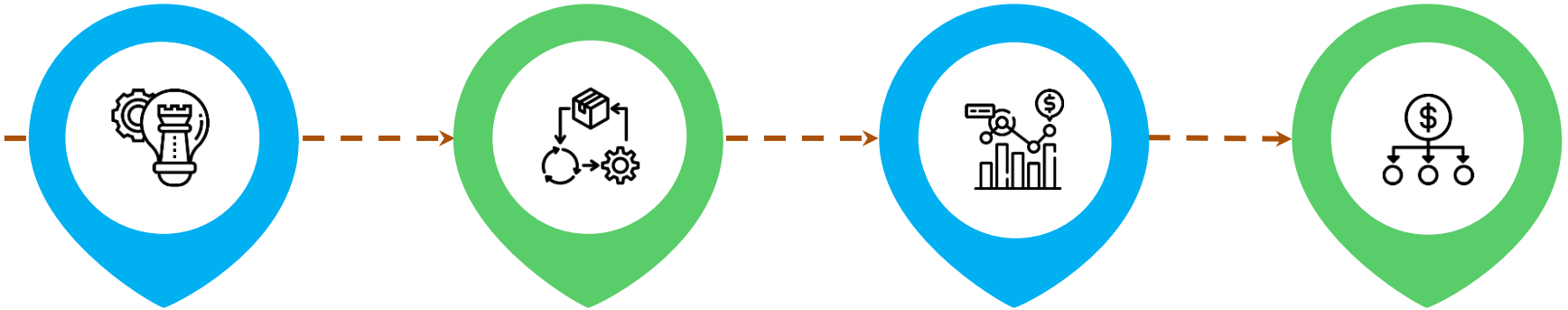
What is it?

Is it relevant?

How does it work?

Target Product Profile:

TPP is a strategic tool that is developed with commercialization in mind. A TPP considers the impact on development, regulatory approval, labeling and successful launch.



Structured Development Framework

Articulates a set of goals, providing focus and guidance for development activities to achieve the desired commercial outcome

Decision Making Tool

Meeting or exceeding these benchmarks can signify high value, leading to approval with speed and improved access to care, while failure may result in early termination.

Roadmap for Drug Development

Roadmap for preclinical and clinical strategies to maximize a product's commercial potential

Deliverables Centric

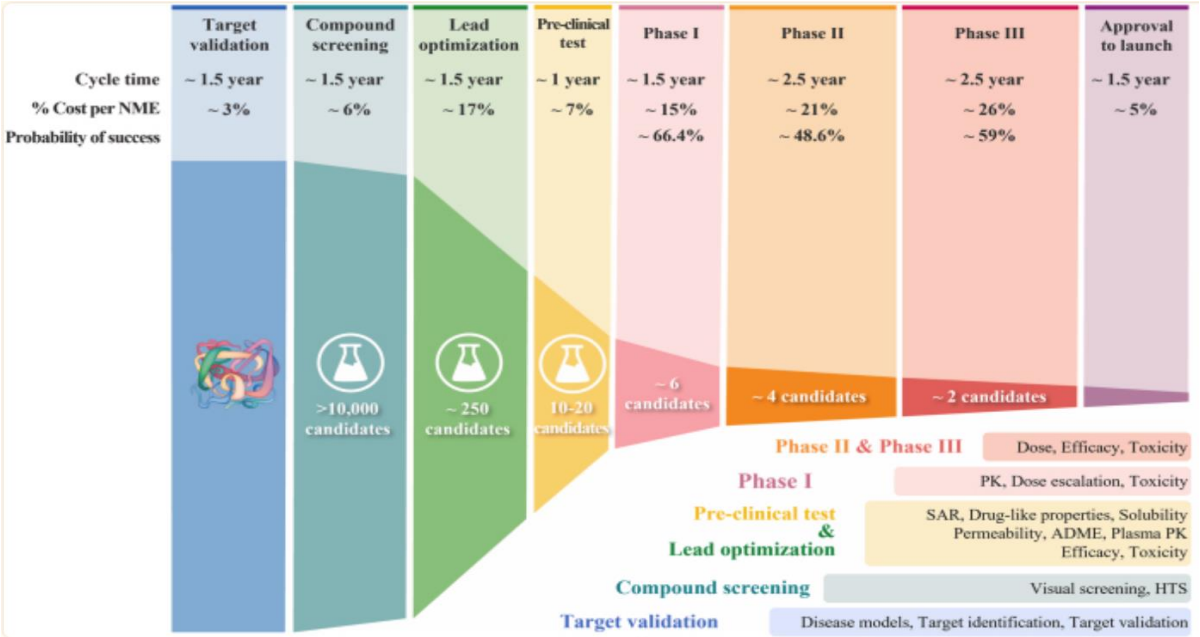
Organized around key sections in the intended drug's labeling, Clinical Plan, Briefing Books.

BioPharma and Biotech Success

Nine out of ten drug candidates fail after they have entered clinical studies during phase I, II, III clinical trials and drug approval.

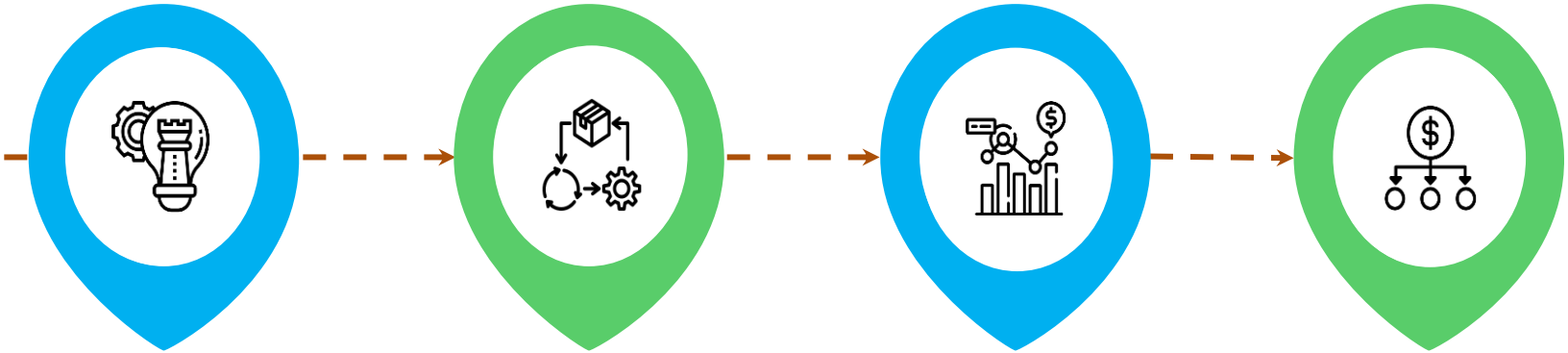
Dowden H., Munro J. Trends in clinical success rates and therapeutic focus. *Nat Rev Drug Discov. 2019; 18:495-496.*

Takebe T., Imai R., Ono S. The current status of drug discovery and development as originated in United States academia: the influence of industrial and academic collaboration on drug discovery and development. *Clinical and translational science*. 2018;11:597–606.



BioPharma and Biotech Success
Four reasons for 90% clinical failures

A regulatory approval is simply an open door to an even riskier stage: commercialization and market access.



Lack of clinical efficacy (40%–50%)

Unmanageable toxicity (30%)

Poor drug-like properties (10% - 15%)

Lack of commercial needs and poor strategic planning (10%)

Target Product Profile (Early Stage/Pivotal Trial)

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Translating differentiating TPP features into measurable attributes

TPP Attributes	Assessment Approach			Development Strategy Impact
	Minimal Acceptable Profile	Ideal Profile	Competitive Profile	
Indication				*High unmet medical need, First in class; clinical stage; competitive landscape review*
Patient Population				Stage of disease, patient journey, Clin Dev Plan (study size, diversity plan, I/E criteria, design, global …)
Dosage Form / Regimen				Monotherapy vs. Combination. Simple versus complex (for patient, HCP, Investigator, etc.
Clinical Efficacy				Primary (approval) and secondary endpoints (differentiation); clinically meaningful difference
Biomarker/Diagnostic				Patient selection, accelerated approval, prior precedence
Safety				Consider adverse effects; special interest to existing therapy
Quality of Life				Payor Value; Differentiation (possible early HTA interactions)
Regulatory Requirement				Acceleration Strategies (ex. Fast Track, BTD, RMAT, Full, Orphan Drug Designation, Conditional MA, PRIME)

NIH: Target Product Profile

1. Example for ischemic stroke- revascularization

Product Targets	Minimum Acceptable Result	Ideal Results
Primary Product Indication	Emergency medicine for acute stroke patients immediately on hospital arrival	Emergency medicine for acute stroke patients in the community even before arrival to a hospital
Patient Population	Adults of all ages with moderate to severe stroke, with potential concurrent use with tPA	Adults of all ages with moderate to severe stroke, with potential concurrent use with tPA or replacement of tPA
Treatment Duration	Acute	Acute
Delivery Mode	IV	IV
Dosage Form	Solution in pre-filled syringes	Solution in autoinjectors
Regimen	Bolus	Bolus
Efficacy	20% or more favorable in comparison to placebo on minimal or no disability 30 days after treatment in patients using Modified Rankin Scale (scores≤1) and NIHSS (scores≤1). Exploratory endpoint: imaging evidence of revascularization	30% or more favorable in comparison to placebo on minimal or no disability 30 days after treatment using Modified Rankin Scale (scores≤1) and NIHSS (scores≤1). Exploratory endpoint: imaging evidence of revascularization
Risk/Side Effect	Devoid of symptomatic intracranial hemorrhage and significant mechanism related adverse effects	Devoid of any symptomatic intracranial hemorrhage and any mechanism related adverse effects
Therapeutic modality	Protein	

Source: https://www.ninds.nih.gov/current-research/research-funded-ninds/translational-research/create-bio/create-bio-application-support-library/create-bio-example-target-product-profile-tpp

Patient-Advocacy Created Target Product Profile Example

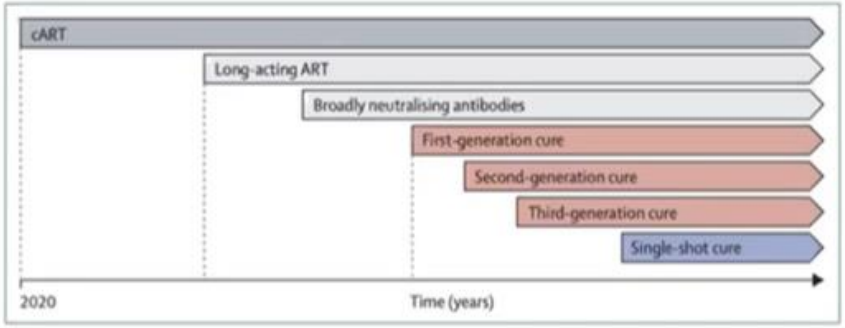

Figure 1: **Timeline of current and future treatments and cures for HIV**
Current and future treatments for HIV. Current treatment for HIV is oral ART. Future options available in the next 1-3 years will probably include long acting injectable antivirals or antibodies. The timing for introduction of HIV cure strategies under investigation currently and an aspirational HIV cure strategy is unknown. ART=antiretroviral therapy.

	Minimum	Optimum
Target Population	Adults >16 to 65 stable on ART	All people living with HIV
Efficacy	Viral load below spec. threshold >20% of ind.	Viral load below detection in >90%
Safety & Tol.	Level of grade 3 dependent on efficacy	No grade 3, 4 events
Dosing & Admin	Oral (preferred) or IV	Single admin, oral preferred
Monitoring	Viral load monitoring	None
Need for Booster	1X a year at most	None
Storage	Cold chain ok	Room temp
Financing	Global Fund, Health insurance	Natl. Governments

Lewin et al. *Multi-Stakeholder Consensus on a Target Product Profile for an HIV Cure* Lancet 2021

Business Relevance: Target Product Profile

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STRATEGIC PLANNING TOOL

- Improves product development and project management
- increase probability of success at later stage

STAKEHOLDER ALIGNMENT

- **Internal**:: R&D, RA, Commercial, Manufacturing
- **External:** Product, Patients, Prescribers, Policymakers, Payers, Partners, Advisors

DECISION MAKING TOOL

- Guiding the protocol design, and analysis of clinical trials
- Better alignment with market needs and customer expectations.

SECURE POTENTIAL FUNDING

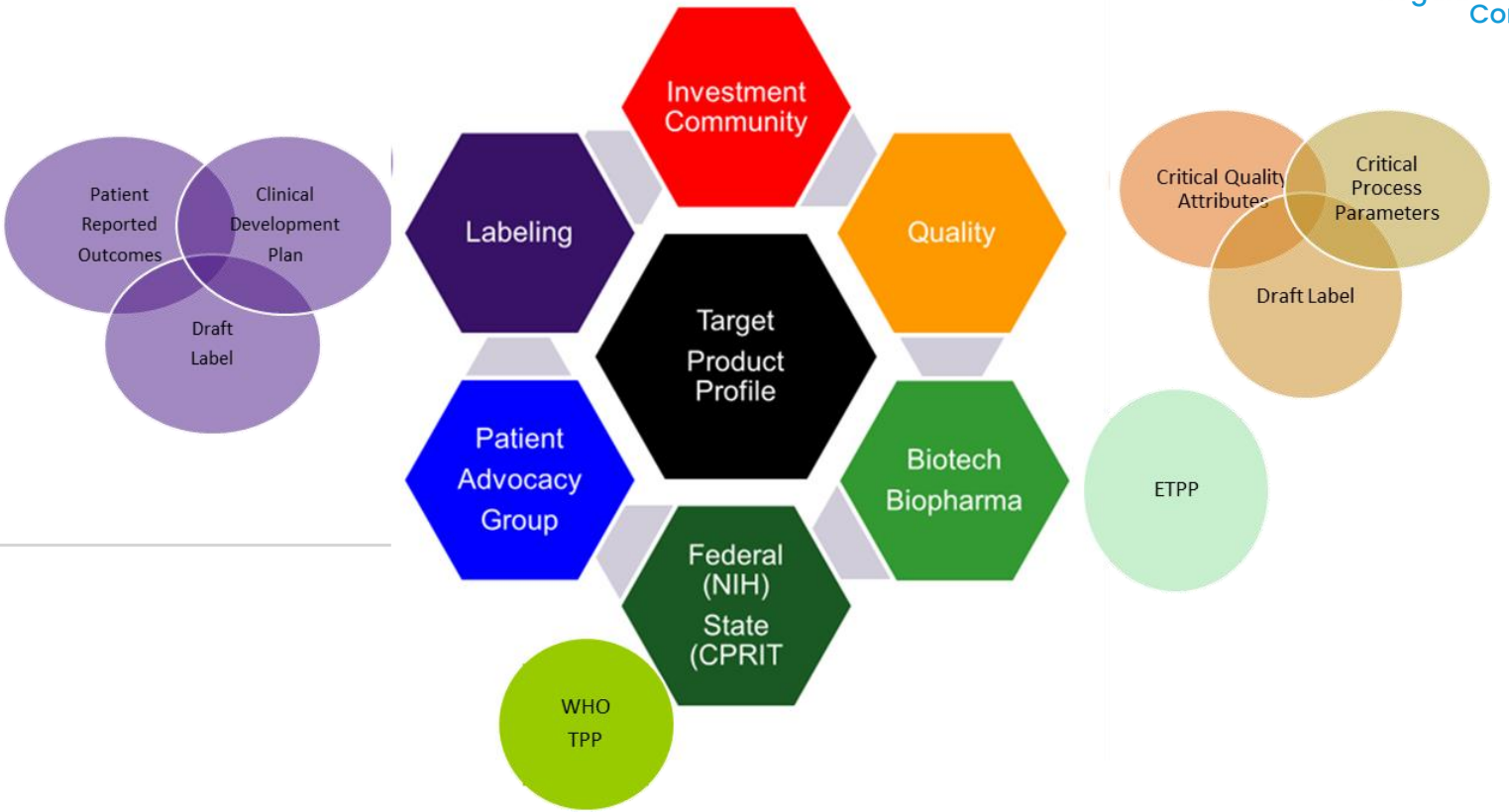
- Summary provides an overview of the product and its goals to aid to secure funding
- Investors/ VCs.

SUPPORTS REGULATORY AGENCY INTERACTIONS

- TPP concepts incorporated into Briefing Documents, Labeling Development

HELP WITH FUTURE DELIVERABLES

- Integrated Development Plan.



Key Takeaways

- TPP contributes to decision-making for funding, successful acquisition and commercial viability
    - Probability of technical success and Probability of regulatory success
- Commercial and Development SMEs work together to create TPP in early-stage
    - FDA and EMA approved products, current clinical guidelines for the intended indications, pharmacologic class and/or biomarkers (e.g. companion diagnostics) and labeling assessment
- TPP guides clinical development program
    - Initial IND General Investigational Plan
    - Outcomes important for patient access/ payer reimbursement

02

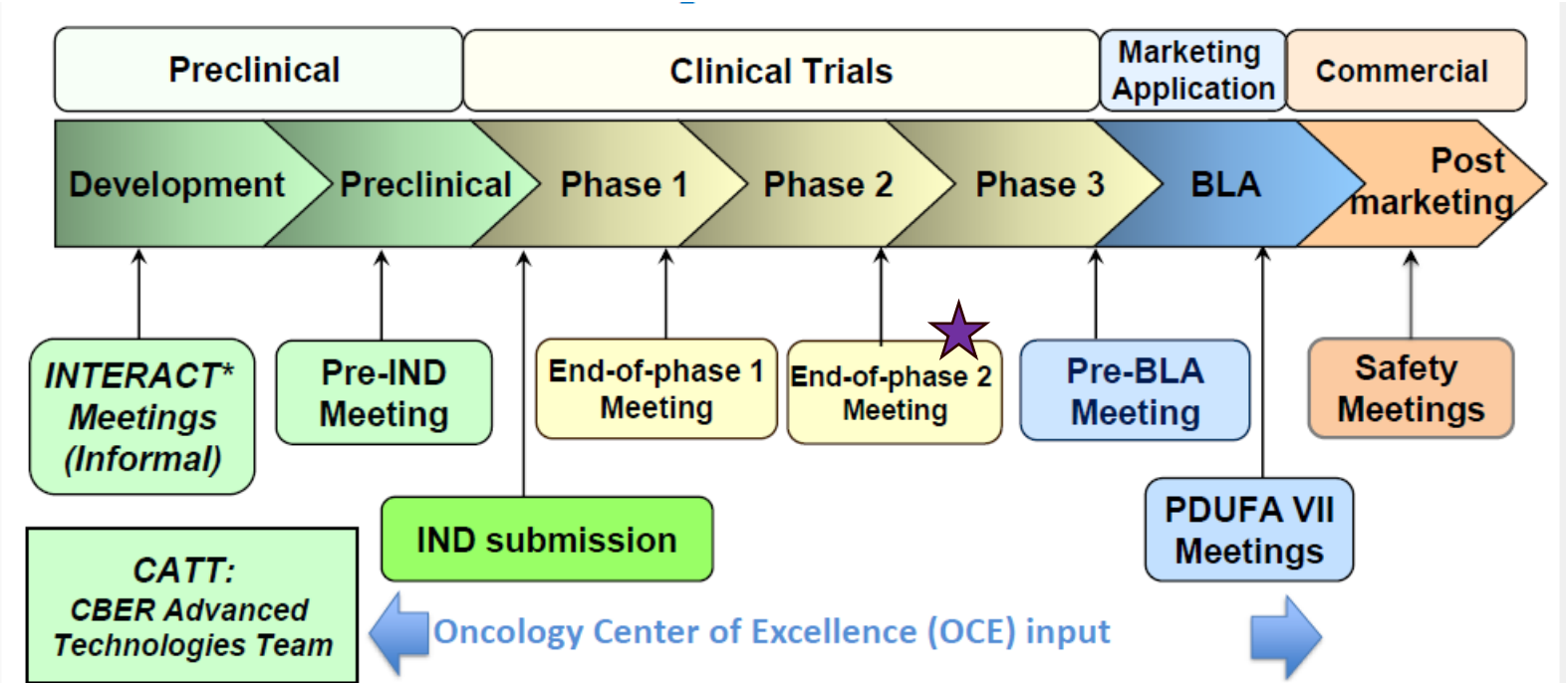
Key Interactions with Regulatory Health Authorities

Engage
Explore
Confirm
Challenges

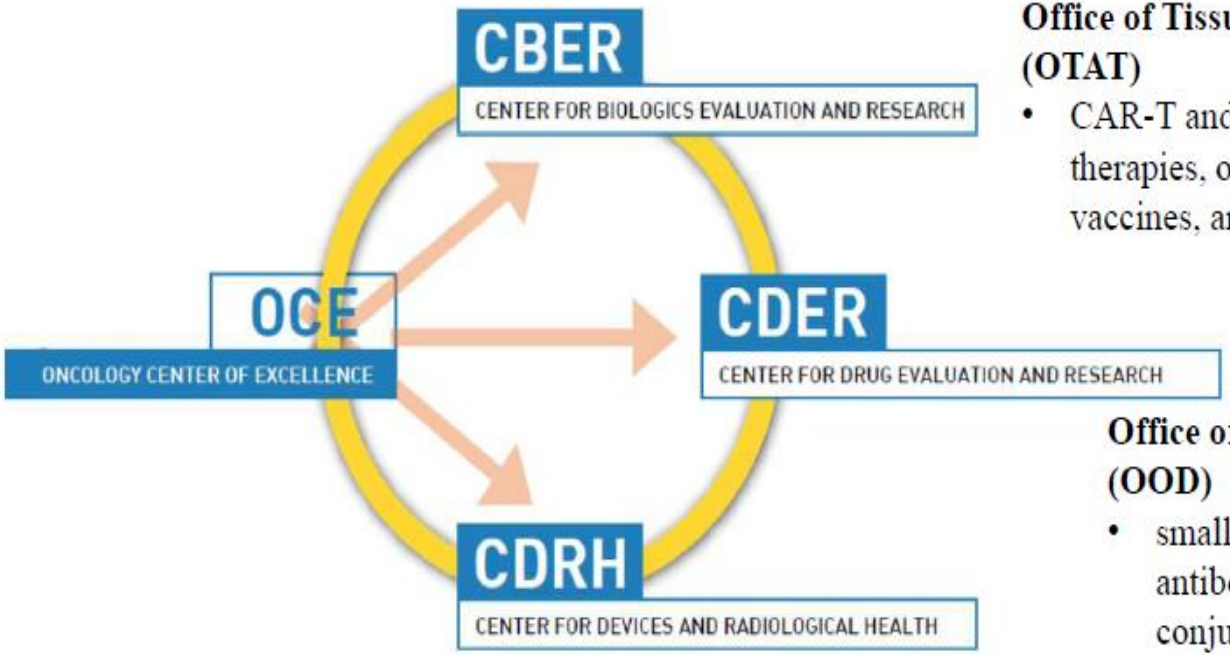
Target Product Profile: Keep The End In Mind

- A dynamic summary that is revised as knowledge about the product grows.
- Facilitates constructive and transparent dialogue with the FDA.
- Guides the design, conduct, and analysis of nonclinical studies and clinical trials for efficient product development.
- Guides the design, conduct, and analysis of drug product, administration
- Embodies the concept of starting with the end goal; outlines labeling goals and supporting studies.

When To Engage FDA During Product Development



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 therapies, oncolytic viruses, therapeutic vaccines, and microbiota

Office of Oncologic Diseases (OOD)

- small molecules, monoclonal antibodies, antibody-drug conjugates

Office of In Vitro Diagnostics and Radiological Health

- companion and complementary diagnostics

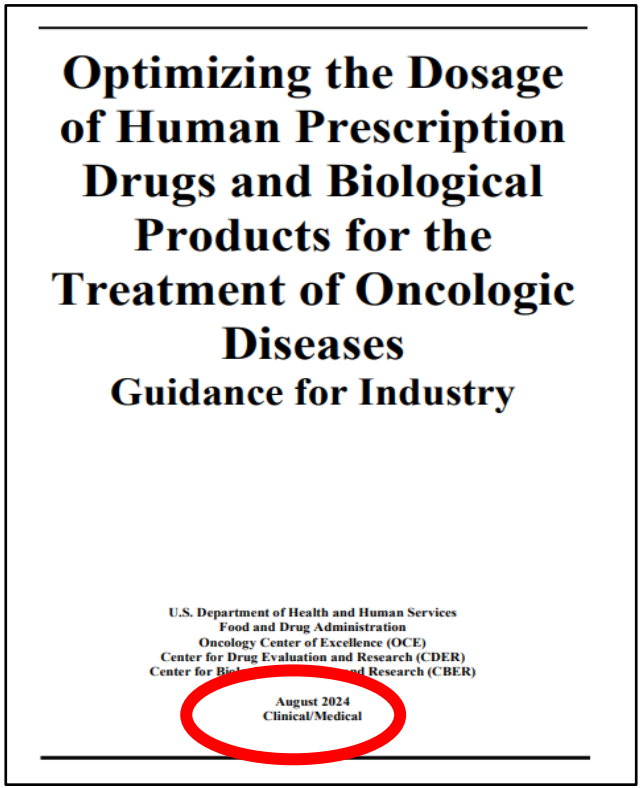
www.fda.gov

Oncology Center of Excellence
Regulatory Policy Projects and Programs Established (~30)

ACE Regulatory Affairs Consulting

Advancing Regulatory Framework For Oncology Product Development

Oncology Dose Optimization



Final Guidance

- Dosage optimization should occur prior to drug approval
- Use the totality of data for dosage selection
  - Including dose- and exposure- response relationships for efficacy and safety
  - Randomized comparisons support identification of optimized dosage(s)
- There is no “one size fits all.” FDA is available to discuss plans

Barriers and Challenges

Barriers to enrollment

- Trial design
- Researcher bias
- Physicians bias
- Exclusion criteria
- Lack of transportation

Swanson et al. *Journal of the National Cancer Institute* 1995

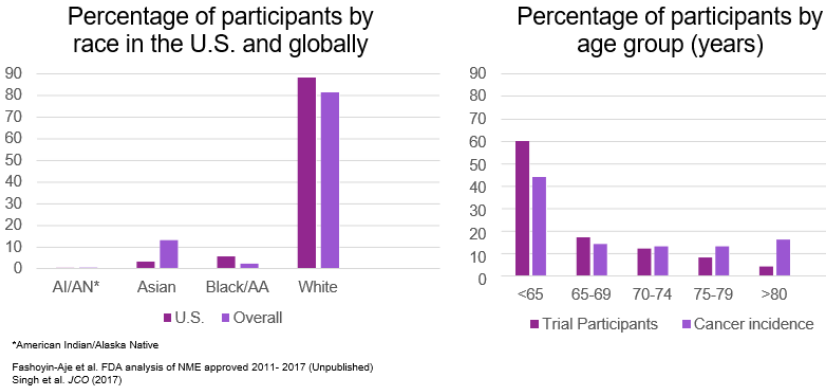
FDA Oncology Therapy Approvals (2008-2018)

Race	Patients enrolled N=70,201
Asian	18%
Black/AA	3%
Hispanic	6%
White	76%

Loree et al. *JAMA Oncol*. 2019

OCE Equity Program

Global Enrollment



*American Indian/Alaska Native

Fashoyin-Aje et al. FDA analysis of NME approved 2011- 2017 (Unpublished)
Singh et al. *JCO* (2017)

OCE's Equity Program: improve representation of historically underrepresented patient populations in cancer clinical trials

- **Project Silver:** improve the evidence base for the treatment of older adults with cancer
- **Project ASIATICA**: bring focus and awareness to Asian American, Native Hawaiian, and other Pacific Islander patients with cancer

OCE Equity Program

Diversity Plans Submitted
April 2022-2023

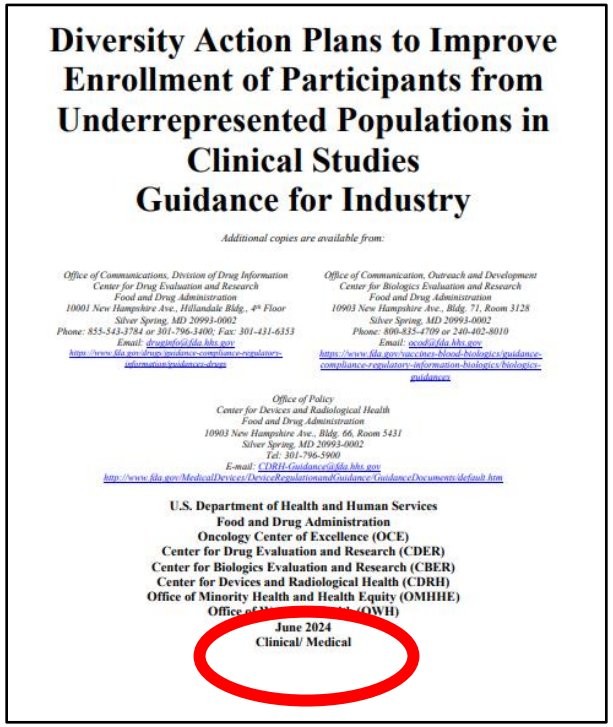
91 submitted to the Centers for Drug Evaluation and Research

76 submitted to oncology divisions

Food and Drug Omnibus Reform Act (FDORA)

- Signed into law December 29, 2022
- Gives FDA the authority to require that sponsors submit Diversity Action Plans that specify their enrollment goals disaggregated by race, ethnicity, sex, and age group
- Diversity should be addressed early in development
- This subsection requires sponsors of any phase 3 or other pivotal drug study to submit diversity action plans study protocol is submitted.
- 520(g)(9) similarly requires sponsors of device trials to submit diversity action plans.
- Exempts submissions made under the expanded access provisions
- Applies to trials of drugs, biological products, and devices, for which enrollment commences 180 days after publication of final guidance on Diversity Action Plans

OCE Equity Program



Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

Office of Policy
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Room 5431
Silver Spring, MD 20993-0002
Tel: 301-796-5900
E-mail: CDRH-Guidance@fda.hhs.gov
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Minority Health and Health Equity (OMHHE)
Office of W... (OWH)
June 2024
Clinical/ Medical

Diversity action plans

(1) the sponsor's goals for clinical study enrollment, disaggregated by age group, sex, and racial and ethnic characteristics;

(2) the rationale for these enrollment goals, including information about the disease or condition and its prevalence or incidence among various demographics;

(3) How the sponsor intends to meet such goals, including demographic specific outreach and enrollment strategies

FDA can waive requirement to submit a diversity action plan

(1) FDA must determine prevalence or incidence of disease or condition being studied makes it impracticable to conduct a clinical trial or

(2) Necessary to protect public health during a public health emergency

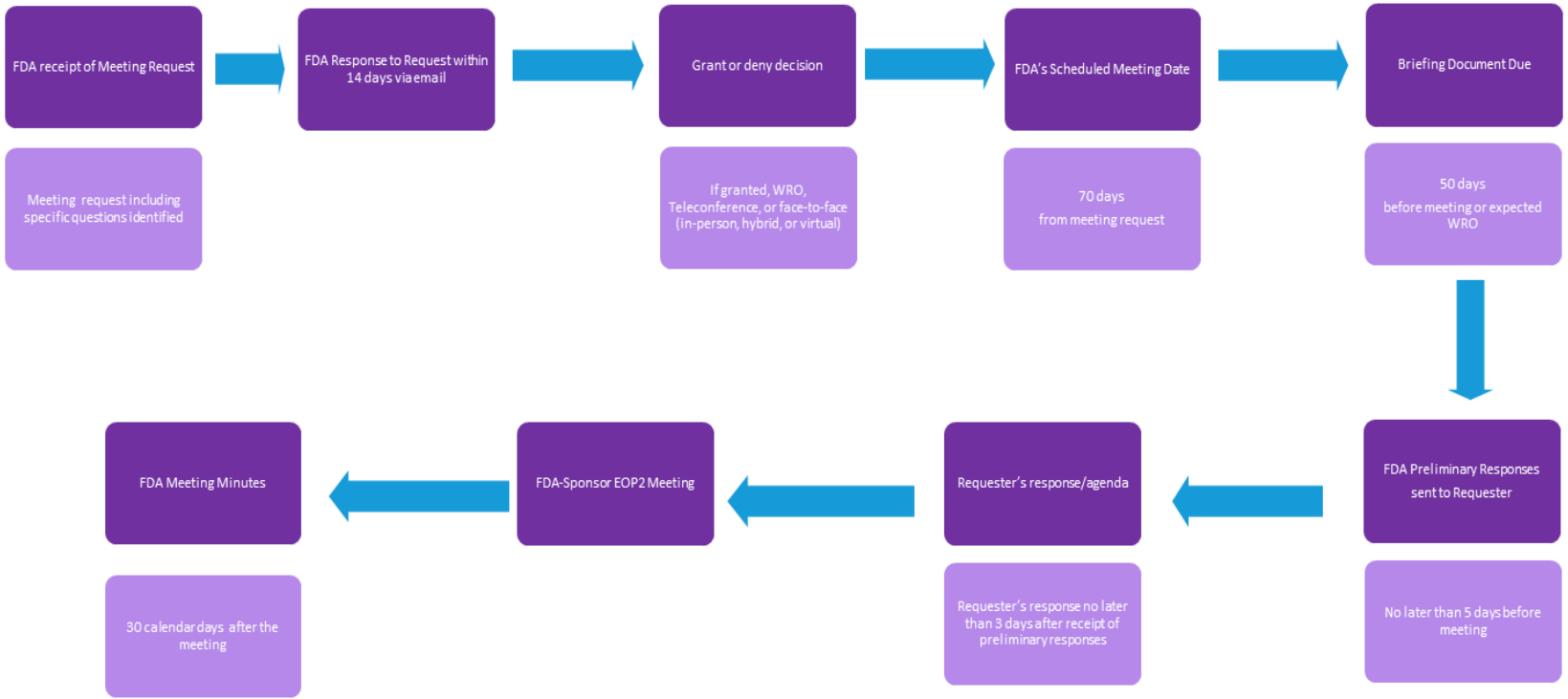
(3) If sponsor requests a waiver, FDA must grant or deny a waiver within 60 days of receiving such a request

PDUFA VII: Sponsor - FDA Meetings Performance Goals

Table 1: Summary of Meeting Management Procedural Goals

Meeting Type	FDA's Response to Request	FDA's Receipt of Meeting Package	FDA's Preliminary Responses to Requester (if applicable)	Requester's Response to FDA's Preliminary Responses (not applicable to WRO)	FDA's Scheduled Meeting Date (days from receipt of request)	FDA's Meeting Minutes to Requester (if applicable)
A	14 days	With meeting request	No later than 2 days before meeting	N/A	Within 30 days	30 days after meeting
B	21 days	No later than 30 days before meeting or expected WRO	No later than 2 days before meeting	N/A	Within 60 days	30 days after meeting
B (EOP)	14 days	No later than 50 days before meeting or expected WRO	No later than 5 days before meeting	No later than 3 days after receipt of Preliminary Responses	Within 70 days	30 days after meeting
C	21 days	No later than 47 days before meeting or expected WRO	No later than 5 days before meeting	No later than 3 days after receipt of Preliminary Responses	Within 75 days	30 days after meeting
C Early consultations on the use of a new surrogate endpoint	21 days	With meeting request; WRO not applicable for these meetings	No later than 5 days before meeting	No later than 3 days after receipt of Preliminary Responses	Within 75 days	30 days after meeting

EOP /Pre-NDA Meeting Request and Workflow



Sponsor Meeting Request Content

III. PDUFA Content of Meeting Requests

A. Should contain:

1. The product name and application number if already assigned;

2. Chemical name, established name, and/or structure (if appropriate). If chemical name and structure is not appropriate, please include a description of your product;

3. Proposed regulatory pathway (e.g., BLA, NDA)

4. Proposed indication or context of product development.

5. Type of meeting being requested (Type A, Type B, Type B(EOP), Type C, Type D, or INTERACT).

6. Dosage form, route of administration, and dosing regimen (frequency and duration).

7. Pediatric study plans, if applicable.

a. Refer to the Policy section of this SOPP (General – number 3) for information on when these are applicable.

8. Human factors engineering plan, if applicable

9. Combination product information (e.g., constituent parts, intended device, intended packaging, planned human factors studies), if applicable.

10. Suggested dates and times (e.g., morning or afternoon) for the meeting that are consistent with the appropriate scheduling time frame for the meeting type being requested. Non-availability dates and times should also be included.

11. A list of proposed questions grouped by FDA discipline. For each question, there should be a brief explanation of the context and purpose of the question.

B. Must Include:

1. Proposed meeting format, e.g., Face-to-Face (in-person or virtual only), teleconference, or written responses only (WRO)

2. The date the meeting background package will be sent by the requester. Note that meeting packages should be included with the meeting request for all Type A, Type C meetings to discuss early consultation on the use of new surrogate endpoints, Type D, and INTERACT meetings.

3. A brief statement of the purpose of the meeting. This statement should include a brief background of the issues underlying the agenda. It also can include a brief summary of completed or planned studies and clinical trials or data that the requester intends to discuss at the meeting, the general nature of the critical questions to be asked, and where the meeting fits in overall development plans. Although the statement should not provide the details of trial designs or completed studies and clinical trials, it should provide enough information to facilitate understanding of the issues, such as a small table that summarizes major results.

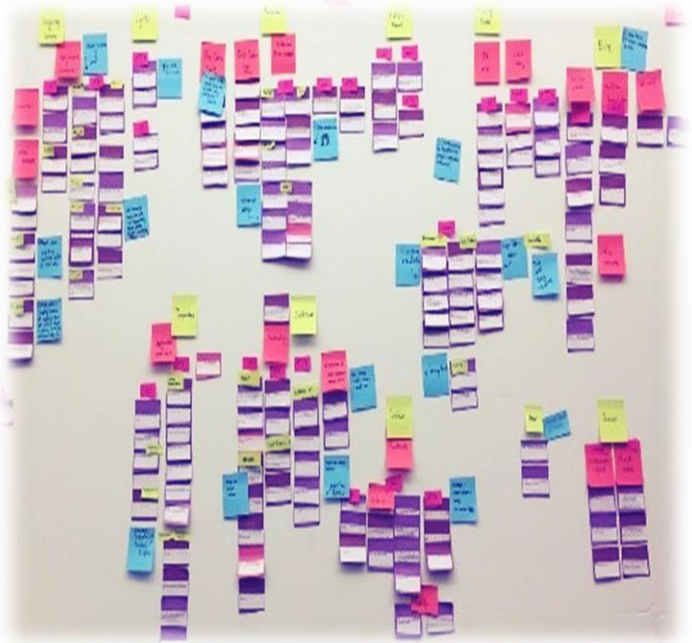
4. A proposed agenda, including estimated times needed for discussion of each agenda item;

5. A list of planned external attendees, including their names and titles. The list should also include the names, titles, and affiliations of consultants and interpreters, if applicable.

6. A list of requested FDA attendees and/or discipline representative(s). Note that requests for attendance by FDA staff who are not otherwise essential to the application's review may affect the ability to hold the meeting within the specified time frame of the meeting type being requested. Therefore, when attendance by nonessential FDA staff is requested, the meeting request should provide a justification for such attendees and state whether or not a later meeting date is acceptable to the requester to accommodate the nonessential FDA attendees.

Pivotal Clinical Trial(s): Prioritization of Questions for FDA Meeting (1-hour)

- Number of pivotal trials
- Dose(s) justification
- Patient Population – pragmatic, I/E, stage of disease, rare disease, diversity action plan, biomarkers, diagnostic,
- Design – pragmatic ex. DCTs
- Accelerated Regulatory Pathway and Designations ex. Breakthrough, Regenerative Medicine Advanced Therapy
- Endpoints – primary endpoints, DHT endpoints, secondary endpoints
- Statistical Analysis Plan
- CMC (typically, separate meeting)
- Special Protocol Assessment
- Etc…..



Meeting Package Content

IV. PDUFA Content of Meeting packages

A. The product name and application number if already assigned.

B. Chemical name and structure (if appropriate). If chemical name and structure is not appropriate, please include a description of your product.

C. Proposed regulatory pathway (e.g., BLA, NDA).

D. Proposed indication or context of product development.

E. Dosage form, route of administration, and dosing regimen (frequency and duration).

F. Pediatric study plans, if applicable.

G. Human factors engineering plan, if applicable

H. Combination product information (e.g., constituent parts, intended device, intended packaging, planned human factors studies), if applicable.

I. A list of all individuals, with their titles and affiliations, who will attend the meeting from the requester's organization, including consultants and interpreters.

J. A background section that includes the following:

1. A brief history of the development program and relevant communications with FDA prior to the meeting;
2. Substantive changes in product development plans (e.g. new indication, population, basis for a combination), when applicable;
3. The current status of product development.

K. A brief statement summarizing the purpose of the meeting and identifying the type of milestone meeting, if applicable.

L. A proposed agenda, including estimated times needed for discussion of each agenda item.

M. A list of the final questions for discussion grouped by FDA discipline and with a brief summary for each question to explain the need or context for the question. Questions regarding combination products should be grouped together.

N. Data to support discussion organized by FDA discipline and question.

1. Protocols, full study reports, or detailed data generally are not appropriate for meeting packages; the summarized material should describe the results of relevant studies and clinical trials with some degree of quantification, and any conclusions about clinical trials that resulted.
2. The trial endpoints should be stated, as should whether endpoints were altered or analyses changed during the course of the trial.

O. Summary information relevant to the product(s) and supplementary information to enable the development of responses to the questions should also be provided. For example:

1. Pre-IND meeting - a summary of manufacturing information including completed or proposed testing and specifications; any pre-clinical studies completed or proposed; any known experience with the product in humans; the proposed eventual clinical use with rationale; a reasonably complete protocol or protocol synopsis; and information on any unique characteristics which differentiate the product from other similar entities.

   The requester is expected to submit their development plan for complying with PREA.
2. End of Phase 1 meeting – a summary of data obtained in the Phase 1 study and the proposed Phase 2/Phase 3 development plan.
3. End of Phase 2/Pre-Phase 3 meeting - a synopsis of data from studies completed to date and proposed Phase 3 protocol(s) including detailed statistical plan. Outlines of any contractual arrangements for product manufacture and details of the characterization of the product to be used in the studies should also be submitted. If the Phase 3 product is not the same as the product intended for the market, proposals for studies to determine the comparability of the products are necessary. The requester is expected to submit their development plan for complying with PREA.

Sponsor Preparation
Know Rules of the Game: Meeting Management

DO's

- Follow strategy and "seek to understand"
- Know relevant FDA regulations, policies and guidances.
  - Proactively consider what may drive FDA positions and anticipate responses
  - Understand external variables that can impact the FDA
- Be transparent and collaborative
- Manage the time during meeting with FDA
  - Maximize time for hearing from FDA

DON'TS

- Discuss any off-agenda items or team playbook
- Do not go beyond the scope of the question. Answer the questions.
- Asking open-ended questions. Sponsors should propose options.
- Hide information or concerns
- Speculate
  - If team does not know, say so and commit to finding out
  - Not all meetings require a response. Okay to take under advisement

Sponsor Preparation
Practice and Scrimmage

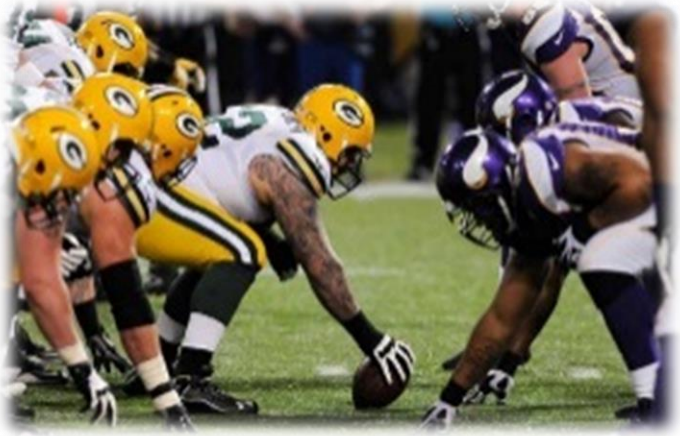
- Sponsor meeting participants rehearse before meeting with FDA
  - Listen to the company spokesperson's response
  - Practice responding to fall back position
- Team rehearsals are important
- Mock FDA Meeting – maybe?
  - Simulate actual FDA meeting to help team be maximally prepared (i.e.. Worse-Case)
  - New participants bring fresh-eyes to help the team
  - Update on changes in external environment (i.e. medical, regulatory agency, policies.

Sponsor Game Time
Play to Win

- Sponsor must reply to FDA preliminary response 3 days before meeting; modify agenda.
- Prepare for “win-win” negotiations
- Be succinct, ask for clarification if needed
- Know limit of what is possible
  - FDA recommendations can be taken under advisement
- State issues positively and assuredly. Speak with a single voice.
- Be transparent and complete as the data presented. The regulatory advice will only be as good as information given.

Sponsor Representatives for FDA Meetings

	Role
Attendee 1	Company Chief Science/Development Officer
Attendee 2	Company Chief Regulatory Affairs Leader
Attendee 3	Company SME Representative based on Questions
Attendee 4	Company SME Representative based on Questions
Attendee 5, 6 … 10	Consultants – Regulatory Affairs, Technical SMEs



Sponsor representatives that will be in attendance

- F2F, Hybrid, Virtual
- Attendees are expected to i.e. FDA comments and questions during the meeting
- Rule of Thumb. Lowest number needed for any meeting format (F2F, Hybrid, Virtual). Cameras on if virtual. Tech support on the ready.
- Non-US citizen participants must be pre-cleared by FDA before attend meetings

Post- Game Analysis: Debrief FDA Meeting

- Debrief immediately following meeting (separate meeting invitation)
  - What happened?
  - What was said?
  - What were “no objections” by FDA?
- Regulatory Affairs is accountable to prepare the FDA meeting summary and distribute to attendees for review/agreement
- Meeting Summary shared to others as appropriate Same day as meeting with FDA
- FDA provides formal minutes of the meeting (INTERACT meetings do not receive formal minutes)

Key Takeaways

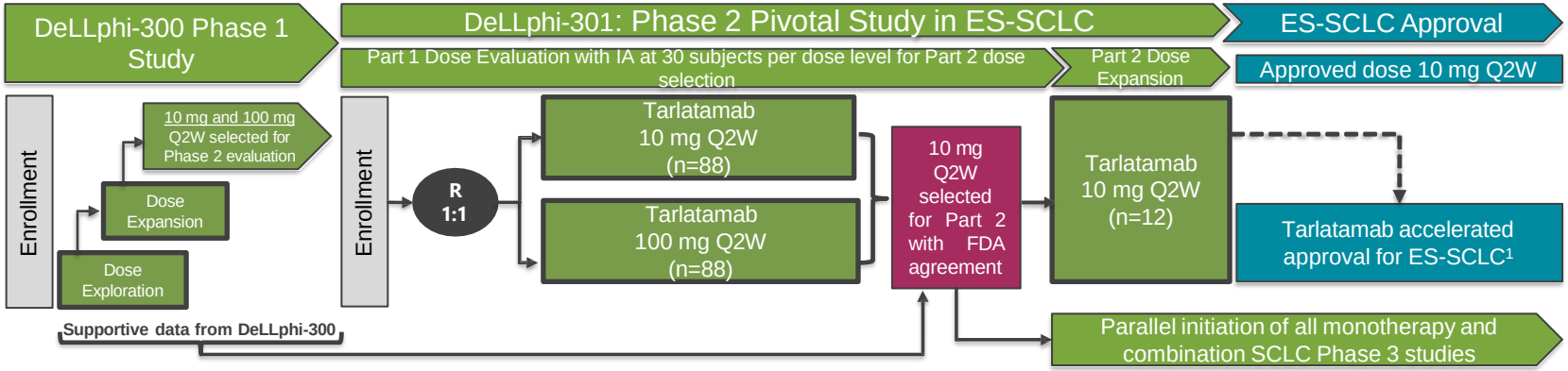
- Ensure internal TPP deliverable are updated and aligned prior to milestone meetings with regulatory authorities (ex. INTERACT, Type D, Pre-IND meeting, Scientific Advice Meetings, etc.)
- Ensure sufficient time, resources are available to engage FDA in meetings.
- Understand criteria for all meeting requests to reduce likelihood of being declined. INTERACT and Type D meetings are most likely to be declined or converted to WRO.
- Regulatory and technology advances are creating swift movement and change in oncology. Be vigilant and rely on regulatory intelligence to plan forward.

03

New Drug Application To Approval

Amgen's Industry Case Study: Implementing OCE Projects in Drug Development

Project Optimus Paradigm: Tarlatamab



Key Takeaways

- Pre-approval dose optimization can strengthen confidence in the labeled dose at marketing authorization, for both patients and providers
- Dose optimization before or during pivotal study can enhance benefit-risk assessment of the drug and streamlines clinical development
  - DeLLphi-301 Phase 2 study not only satisfied Project Optimus requirements but also efficiently generated registration data package to support accelerated approval of tarlatamab-dlle for ES-SCLC
- Early dose optimization can accelerate clinical development by enabling simultaneous initiation of multiple studies

ES-SCLC: Extensive Stage Small-Cell Lung Cancer; Q2W: Once every 2 weeks
[1] treatment of adult patients with ES-SCLC with disease progression on or after platinum-based chemotherapy

Early Dose Determination Expedited Tarlatamab Clinical Development

- Tarlatamab dose selection in the pivotal Phase 2 study (DeLLphi-301) enabled simultaneous initiation of three Phase 3 studies in monotherapy and combination setting in late and earlier line in SCLC

Tarlatamab 10 mg Q2W dose from DeLLphi-301 was implemented in all Phase 3 studies

Phase 3 Combination (tarlatamab + durvalumab) 1L Maintenance ES-SCLC (DeLLphi-305)

Totality of data from following studies supported dose selection (tarlatamab 10mg Q2W + durvalumab):

- DeLLphi-303 (1L): Ph1b tarlatamab + anti- PD-L1 inhibitors (durvalumab and atezolizumab)
  - Tarlatamab maintenance doses evaluated: 10 mg Q2W
  - Efficacy: n=20; Safety: n=36
- DeLLphi-301 (3L): Ph2 pivotal tarlatamab monotherapy
  - Doses evaluated: 10 mg and 100 mg Q2W
  - Efficacy and Safety: n=30 (1:1 randomization)
- DeLLphi-300 (2L+): Ph1 FIH tarlatamab monotherapy
  - Doses evaluated: 0.003 mg to 100 mg Q2W (10 dose levels)
  - Efficacy: n=156; Safety: n=176

Additional Rationale

- Prior agreement with FDA for tarlatamab 10 mg Q2W in combination with anti-PDL1 inhibitors (durvalumab and atezolizumab) in DeLLphi-303

Phase 3 Monotherapy LS-SCLC (DeLLphi-306)

Totality of data from following studies supported dose selection (tarlatamab 10mg Q2W):

- DeLLphi-301 (3L): Ph2 pivotal tarlatamab monotherapy
  - Doses evaluated: 10 mg and 100 mg Q2W
  - Efficacy and Safety: n=30 (1:1 randomization)
- DeLLphi-300 (2L+): Ph1 FIH tarlatamab monotherapy
  - Doses evaluated: 0.003 mg to 100 mg Q2W (10 dose levels)
  - Efficacy: n=156; Safety: n=176

Additional Rationale

- Similarity of tumor biology and patient characteristics across all stages of SCLC

Phase 3 Monotherapy 2L SCLC (DeLLphi-304)

Totality of data from following studies supported dose selection (tarlatamab 10mg Q2W):

- DeLLphi-301 (3L): Ph2 pivotal tarlatamab monotherapy
  - Doses evaluated: 10 mg and 100 mg Q2W
  - Efficacy and Safety: n=30 (1:1 randomization)
- DeLLphi-300 (2L+): Ph1 FIH tarlatamab monotherapy
  - Doses evaluated: 0.003 mg to 100 mg Q2W (10 dose levels)
  - Efficacy: n=156; Safety: n=176

ES-SCLC: Extensive Stage Small-Cell Lung Cancer; FDA: Food and Drug Administration; FIH: First-in-human; LS-SCLC: Limited Stage Small-Cell Lung Cancer; Q2W: Once every 2 weeks

Project Equity – Enhancing Enrollment of Underrepresented Racial and Ethnic Populations

- Amgen implemented following measures to enhance enrollment of underrepresented racial and ethnic populations across programs
- Despite implementing the outlined strategies, Amgen could not meet the pre-determined target and will need to complete the postmarketing commitment

Strategic Measures

- **Direct Patient input** to inform study design
- **Targeted country/site** selection to enhance participation
- **Patient advocacy engagement** for clinical trial awareness
- Use of **patient recruitment vendors** to geolocate community sites near existing trial sites

Additional Approaches

- Conducted **educational SCLC workshops** in targeted cities with patient advocacy group
- Identified **partner sites** for potential Phase 3 program inclusion
- Instituted **Diversity Steering Committee** to address enrollment barriers

Dedicated resources

- Established Representation in Clinical Research (**RISE**) program
- Appointed a dedicated **Site Engagement Lead**

Project Orbis: Amgen's Experiential Perspective

- Amgen has utilized Project Orbis for four applications across three products to date
  - Sotorasib (2021), Tarlatamab (2023), Blinatumomab (2022, 2023)
- For these applications, Amgen collaborated with a range of 2-6 Project Orbis Partners (POPs) per application under Type A, B, or C Project Orbis
  - Australia, Brazil, Canada, Great Britain, Israel, Singapore, and Switzerland

What Worked Well

- Early planning for Project Orbis in case of acceptance
- Timely scheduling of pre-submission meetings with POPs to enable participation
- POPs attendance at FDA orientation meeting enabled collaborative data package discussions
- Sharing POP review correspondence among POPs minimized redundant RFIs

Benefits for Sponsors

- Utilization of similar data package in all POPs
- Substantially fewer RTQs vs non-Project Orbis submissions
- Likely consistent labelling and PMR/PMCs across POPs
- Potential for earlier approval by POPs vs non-Project Orbis submissions

Participation Considerations

- Outstanding clinical trial results
- Acceptability of similar data package by POPs
- Adequate resources for simultaneous RTQs and label negotiations across multiple countries
- If supplement, consider ongoing review of other efficacy supplements

FDA: Food and Drug Administration; PMC: Postmarketing Commitment; PMR: Postmarketing Requirement; RTQ: Response to Question

Project Confirm: Amgen's Drive to Expedite Confirmatory Studies

- Amgen is committed to accelerating confirmatory study completion, in alignment with Project Confirm
  - Tarlatamab: ~88% enrollment completed in the confirmatory study (DeLLphi-304) at the time of BLA approval
- Following key strategies were employed to boost enrollment in the tarlatamab confirmatory study

Broad Geographic Footprint

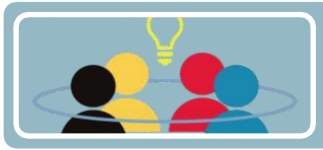
- Activation of multiple sites across countries to minimize start-up delays

Site Contracting

- Implementation of measures for streamlined negotiations and faster execution

Optimized Country/Site Selection

- Utilization of advanced data analytics



PI Engagement

- Elevated PI engagement and enthusiasm through regular data sharing

BLA: Biologics License Application

FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer (press release)

On May 16, 2024, the Food and Drug Administration granted accelerated approval to tarlatamab-dlle (Imdelltra, Amgen, Inc.) for extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy.

Efficacy and Safety

- Efficacy was evaluated in 99 patients with relapsed/refractory ES-SCLC with disease progression following platinum-based chemotherapy enrolled in DeLLphi-301 [NCT05060016], an open-label, multicenter, multi-cohort study…
- The major efficacy outcome measures were overall response rate (ORR) per RECIST 1.1 and duration of response (DOR), as assessed by blinded independent central review. ORR was 40% (95% CI: 31, 51) and median DOR was 9.7 months (range 2.7, 20.7+). …
- Boxed Warning for serious or life-threatening cytokine release syndrome (CRS) and neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS). The most common adverse reactions (>20%) were cytokine release syndrome (CRS), …

Expedited Programs

- This review was conducted under Project Orbis, … with the Brazilian Health Regulatory Agency (ANVISA), Health Canada (HC), Israel's Ministry of Health (IMoH), and United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA).
- This review used the Real-Time Oncology Review (RTOR) pilot program, which streamlined data submission prior to the filing of the entire clinical application, and the Assessment Aid, a voluntary submission from the applicant to facilitate the FDA's assessment.
- The FDA approved this application 1 month ahead of the FDA goal date.
- This application was granted priority review, breakthrough designation, and orphan drug designation.

Key Takeaways

- Sponsor-FDA collaboration takes more interaction
- Communication, coordination and high-performance team are essential during the application review phase.
- Expedited development tools provide speed to Agency action, however, more resource intensive on Sponsor.
- Global submission can facilitate faster review; increase probability of regulatory success
- Planning for commercial launch is more efficient and effective.
- Faster time to market and patients

04

Launch
and
Post Approval

Risk
Reward
On-Market Compliance

"It's not hyperbole to suggest that emerging biopharma companies (EBPs) hold the keys to the success of the entire healthcare ecosystem. …

… A failure to have a strong launch leads to poor results and ultimately a failure of both product and company. There's a lot on the line with that first product."

~ Francis Pollaro [1]

[1] Francis Pollaro. Biopharma's Untapped Value: The Quest to Reverse First-Launch Failure Trends. Pharmaceutical Executive 12-01-2022 Volume 42: Issue 12. https://www.pharmexec.com/view/biopharma-s-untapped-value-the-quest-to-reverse-first-launch-failure-trends

OPDP Promotional Untitled Letter and Warning (FDA Law Blog)

- Untitled Letter was issued to Mirati Therapeutics Inc. (Mirati), a Bristol Myers Squibb company, on August 1, 2024 for content on a healthcare provider branded website for its product, KRAZATI (adagrasib), which was approved under FDA's accelerated approval pathway for patients with certain types of non-small cell lung cancer based on objective response rate (ORR) and duration of response (DOR).
- The Mirati letter deals with much more nuanced issues than the letter to kaleo. When dealing with a drug that is approved via the accelerated approval pathway, can efficacy data be presented as consistent with the FDA-required labeling (CFL) and be subject to the "scientifically appropriate and statistically sound" (SASS) standard, generally thought to be a lesser substantiation standard than the traditional regulatory requirements of "substantial evidence" and "substantial clinical experience?" Even in a CFL world, these presentations likely fall short of the SASS standard where the communication "relies on a study that is inadequate to support the representations or suggestions it presents [and] disclosure of the material limitations of that study does not correct the misleading message conveyed by the communication."
- KRAZATI was approved under the accelerated approval pathway, Mirati would have been required to submit all promotional materials for the drug thirty (30) days in advance of the material being used. As FDA did not object to the timing of the submission in the letter, it seems that FDA (likely) received a copy of this website for review, FDA did not comment, and Mirati moved forward with publishing – only to receive an Untitled Letter months later.

Key Takeaways

Post-Marketing Requirements (ie. accelerated approval, PREA) and Post-Marketing Commitments (ex. Diversity Action Plan) must be completed.

Promotional claims (ex. Untitled Letters; Warnings)

Safety reporting (ex. REMS)

Agenda

ACE Regulatory Affairs Consulting

01

Target Product Profile

02

Key Interactions with Regulatory Health Authorities

03

New Drug Application To Approval

04

Launch and Post Approval

“Every accomplishment starts with a decision to try.”

~ John F Kennedy

“Begin with the end in mind.”

~ Stephen Covey

“The sea is dangerous and its storms terrible, but these obstacles have never been sufficient reason to remain ashore...unlike the mediocre, intrepid spirits seek victory over those things that seem impossible... it is with an iron will that they embark on the most daring of all endeavors... to meet the shadowy future without fear and conquer the unknown.”

~ Ferdinand Magellan

THANK YOU!

Cheryl Beal Anderson, PharmD MBA
ACE Regulatory Affairs Consulting
Founder & CEO

Acceleration Pathways. ACE RAC seeks regulatory pathways that accelerate development for drugs and therapeutics, with rare disease, for people living with cancer, psychiatric and neurodegenerative diseases.

Collaborative Communications. ACE RAC is seasoned, and guides sponsors approaches, requests, and regulatory briefing documents to meet with its key stakeholder FDA for meaningful outcomes through active listening and execution with impeccable quality.

Excellence and Engagement. ACE RAC brings 25+ years of "know-how," "know-who, " and "know-why." We are engaged to support the next generation of innovative biotech and biopharma products to market, leveraging all available tools to reach patients with the disease, including those from underrepresented and underserved patient groups

Back-up

What Are Examples of INTERACT Meeting Topics

- Choice of preclinical models, toxicology studies, and design of proof-of-concept (POC) studies
- Chemistry, manufacturing, and controls strategies to demonstrate product safety to support first in human (FIH) studies
- Clinical trial recommendations for FIH studies in clinical population

INTERACT Meeting Package: Best Practices for CMC

- A summary or high-level description of the product, its manufacturing process and the proposed characterization and lot release tests.
- The sponsor's position and justification for all of the sponsor's questions.
- References to published information related to the product, along with copies of the publications.
- A comprehensive summary of all preclinical (in vitro and in vivo) studies conducted thus far using the intended clinical product, and the results obtained.
- Contributions from publications that the sponsor considers relevant to their program should be integrated into this summary, and copies of each publication should also be provided.

OTP recommends that sponsors refer to:
Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

•Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)

INTERACT Meeting Package: Best Practices for Pharm/Tox

- A comprehensive summary of all preclinical (in vitro and in vivo) studies conducted thus far using the intended clinical product, and the results obtained.
- Contributions from publications that the sponsor considers relevant to their program should be integrated into this summary, and copies of each publication should also be provided.
- A detailed discussion, with protocol outlines, regarding the additional preclinical proof-of-concept studies the sponsor thinks they need to conduct to adequately support administration of the intended clinical product in the target patient population.
- The sponsor's position and justification for all questions the sponsor poses.
- Questions regarding definitive preclinical safety studies are discussed in the pre-IND meeting and should not be included in the INTERACT package.

OTP recommends that sponsors refer to: "Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products."

INTERACT Meeting Package: Best Practices Clinical

- Clinical comments are generally high-level recommendations, and do not focus on details of a specific clinical protocol.
- the disease of interest
- target study population
- available natural history information/data on the condition
- available treatment options for condition
- brief outline of first-in-human study

OTP recommends that sponsors refer to the FDA guidance "Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry."

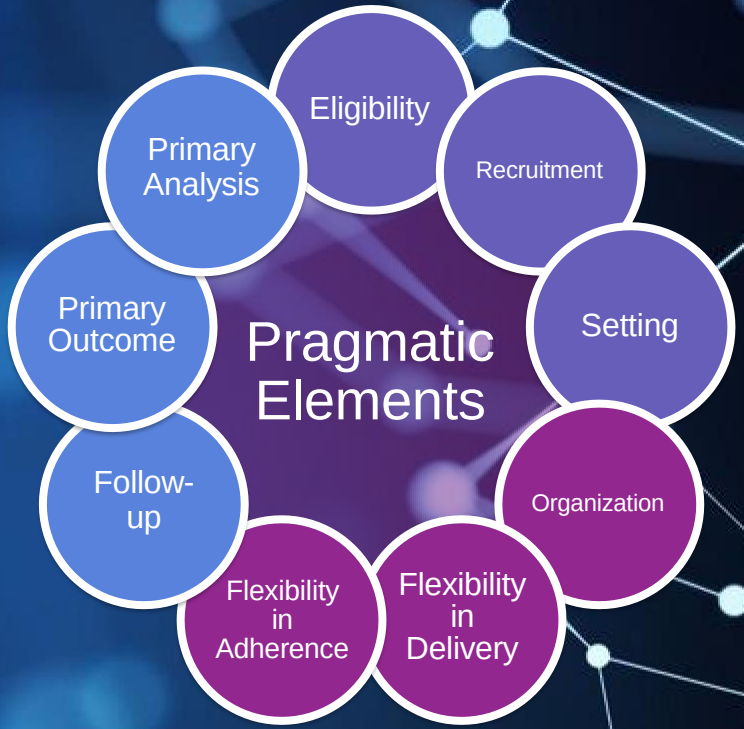
INTERACT Meeting Package: Commons Reasons for Denial

- The meeting package is substantially deficient, significantly limiting the ability to provide constructive feedback.
- Questions about whether a product regulated as a drug, device, biological product, combination product or under Section 361 of the PHS Act and regulations in 21 CFR Part 1271
- The stage of the product development program is premature
  - does not specify the investigational clinical product.
  - does not provide preclinical proof-of-concept (POC) or other pilot data.
  - has not conducted any preclinical studies (e.g., POC studies) with their intended clinical product.
- The stage of the product development program is too advanced
  - POC, some safety studies completed and at the point of design/ conduct of definitive toxicology studies
  - the manufacturing process, assays and release criteria for the clinical studies are developed
  - same or a similar platform as for other product(s) submitted to OTP by the same sponsor.
  - clinical data exist from previous studies for the same product and clinical indication.

OCE Project Pragmatica

Traditional clinical trials are typically associated with significant monitoring, assessments, tests, and clinical follow up visits that can be burdensome to trial participants, investigators, and trial sponsors

Project Pragmatica seeks to introduce efficiencies and enhance patient centricity by integrating aspects of clinical trials with real-world routine clinical practice.



Pragmatic Clinical Trials

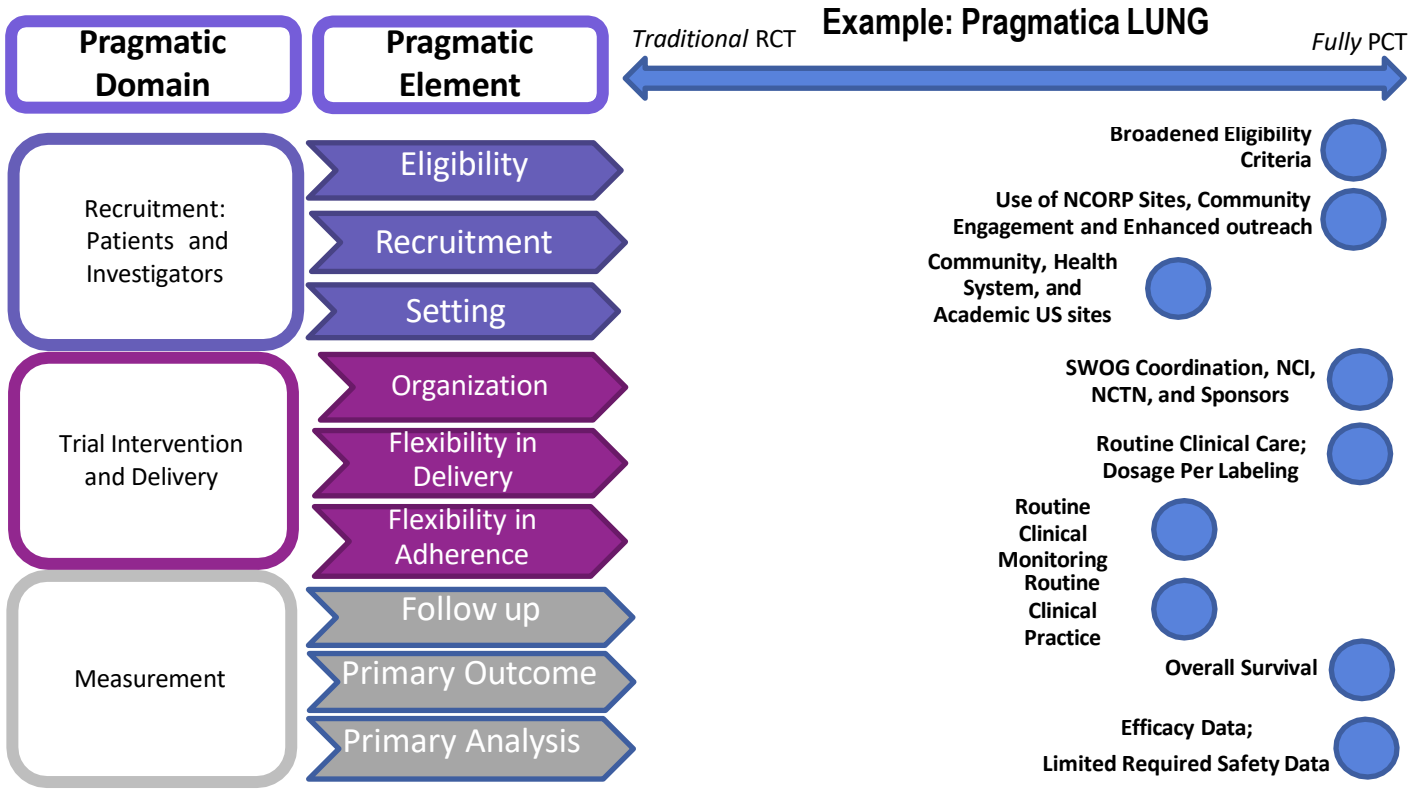
- May incorporate design elements that are more **reflective of routine clinical practice**.
- May take advantage of efficiencies such **as simpler eligibility criteria** and flexibilities in trial delivery and outcome measurement
- **Degree of flexibility tailored** to trial context, with patient safety at forefront
- More **"real-world" setting can reduce burden** of trial participation, with hope to facilitate more diverse trial populations, rapid enrollment and reduced attrition.
- Pragmatic trials may have potential to result in evidence that is **more broadly representative** of the general population.

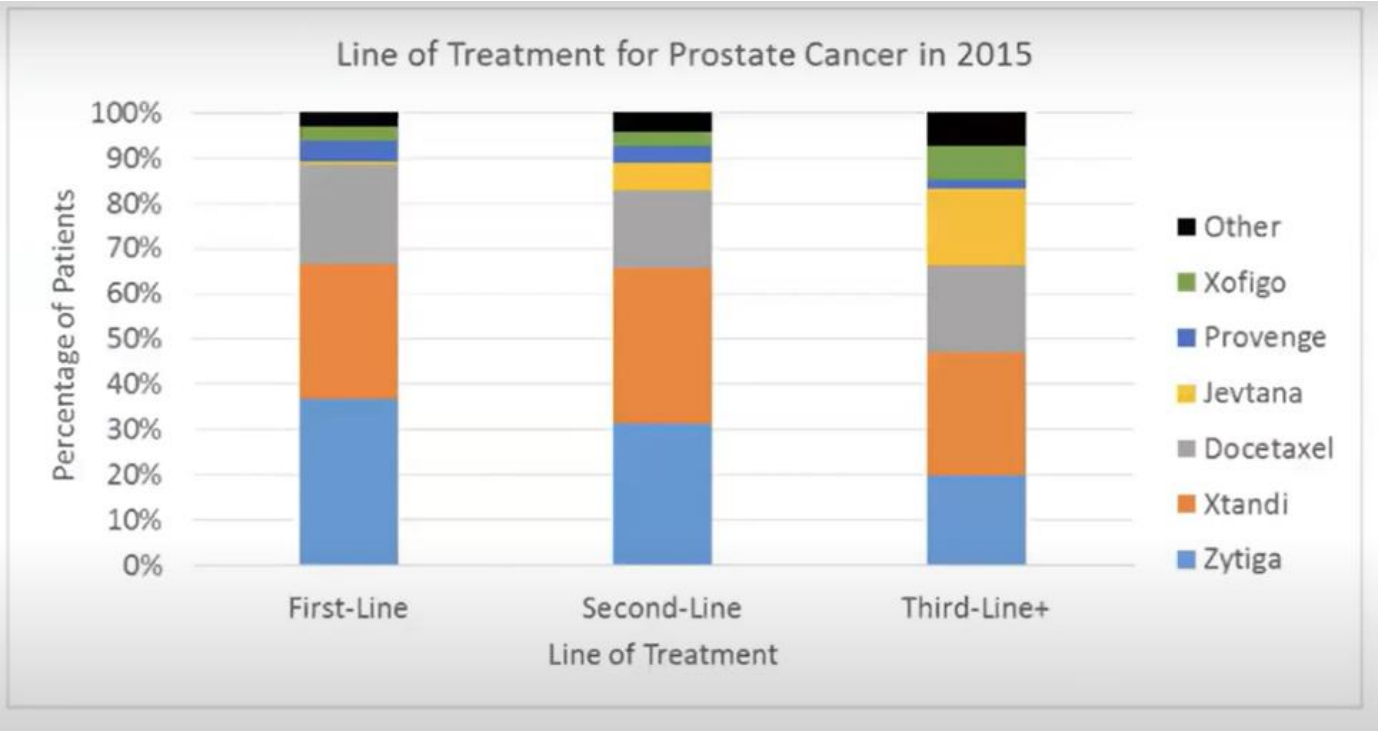
Pragmatic Elements

Design features that can be integrated into a clinical trial, including but not limited to ≥1 of the following:

- broad eligibility criteria
- simplified recruitment and follow-up
- flexibility in delivery of the intervention
- flexibility in assessment frequency
- measurement of outcomes

Adapted from Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clinical Trials. 2015;12(5):436-441.doi:10.1177/1740774515598334


Pragmatic Domain
Pragmatic Element
Traditional RCT
Example: Pragmatica LUNG
Fully PCT
Recruitment: Patients and Investigators
Eligibility
Recruitment
Setting
Trial Intervention and Delivery
Organization
Flexibility in Delivery
Flexibility in Adherence
Measurement
Follow up
Primary Outcome
Primary Analysis
Broadened Eligibility Criteria
Use of NCORP Sites, Community Engagement and Enhanced outreach
Community, Health System, and Academic US sites
SWOG Coordination, NCI, NCTN, and Sponsors
Routine Clinical Care; Dosage Per Labeling
Routine Clinical Monitoring
Routine Clinical Practice
Overall Survival
Efficacy Data;
Limited Required Safety Data



Jafari J, Target Product Profile (TPP) Development and Overview Best Practices. Webinar Mar 2023

Brand Name	Generic Name	Company	MOA	Stage of Disease	Price per year	2015 WW sales
Zytiga	Abiraterone	Janssen	Anti-androgen	mCRPC	$105 k	**$2.23 B**
Xtandi	Enzalutamide	Astellas/Medivation	Anti-androgen	mCRPC	$114 k	**$1.91 B**
Provenge	Sipuleucel-T	Dendreon (Valeant)	Cancer vaccine	Asymptomatic/minimally sympotomatic mCRPC	$121 k (for three doses)	**$250 M**
Xofigo	Radium-223	Bayer	Alpha radiation	mCRPC with symptomatic bone metastases and no visceral metastatic disease.	$129 k (for six doses)	**$283 M**
Jevtana	Cabazitaxel	Sanofi-Aventis	Microtubule inhibitor	mCRPC, previously treated with docetaxel	$57 k (for six cycles)	**$354 M**
Taxotere	Docetaxel	Sanofi-Aventis	Microtubule inhibitor	Hormone refractory metastatic prostatic cancer	$24 k (for six cycles)	**$245 M**
Lupron	Leuprolide Acetate	AbbVie	GnRH agonist	Advanced prostate cancer	$15 k	**$826 M**

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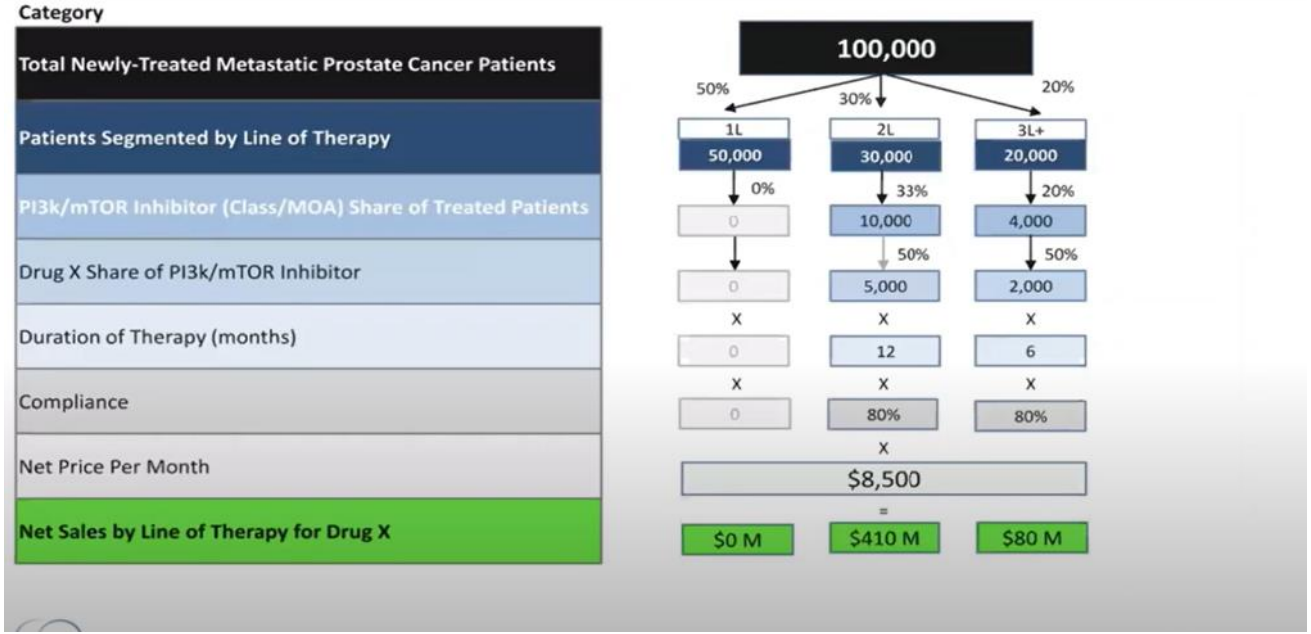
Estimating the Size of the Opportunity for a Novel Therapy in the US Prostate Cancer Market



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