Clinical Research Study, Management & Compliance

Investigational New Drug Committee (INDC)

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Agenda

- IND Overview
- Investigator vs Sponsor Responsibilities
- MSK Structure
- IND/IDE applications at MSK
- FDA Review & Reporting
- Resources

IND Overview

What is an IND?

- “Investigational New Drug” application
- Clearance by the FDA to use a drug product not previously authorized for marketing in the United States
- Applies to new drugs, new antibiotics and new biologics

What is the legal basis for an IND?

- Law governing development of new drugs in the U.S. (Federal Food, Drug and Cosmetic Act (FD & C Act))
- Requirements of the FD & C Act:
  - Proof of safety
  - Substantial evidence of efficacy
  - Informative labeling for the product
  - Demonstration of manufacturing of the product to the desired strength, quality, purity and identity
  - Signed agreement from investigators

Investigator vs Sponsor Responsibilities

Investigator Responsibilities- 1572 Form

Investigator(s)= The individual(s) conducting the trial

- Statement of investigator
- Legally binding contract with the FDA
- Personally conduct study in accordance with the protocol
- IRB approval required prior to making any changes to the research
- Promptly report any changes and unanticipated risks to IRB

Sponsor Responsibilities

Sponsor = Responsible for ALL aspects of the IND!

- Submits IND application to FDA
- Oversees all associated clinical trials and investigators
    - Ensure investigation is conducted according to the general investigational plan/protocol
- Fulfills reporting requirements
    - Annual Reports
    - Significant new adverse effects/risks
- Ensure proper monitoring

For an MSK IND application, the sponsor is MSK not the investigator

YOUR TURN!

- IN THE CHAT, as an investigator can you be the sponsor of an IND?
  - Yes
  - No

NO
MSK is the sponsor for all MSK held INDs

MSK Structure

Regulatory Oversight and Product Development Office

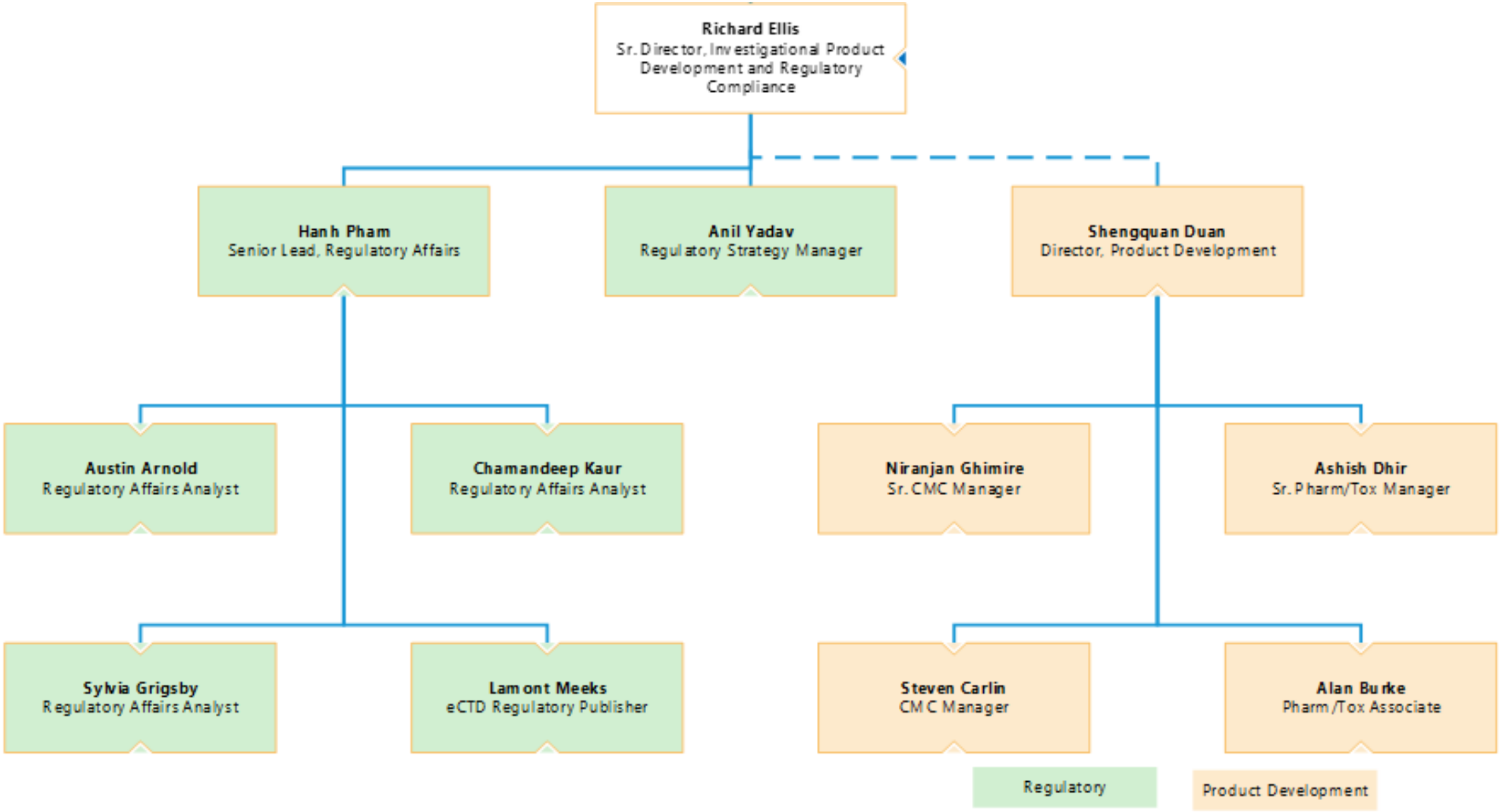
Product Development Office (PDO)

- Guidance-development strategy and preclinical requirements
- Preparation of IND applications/technical documents

IND Office (INDO)

- MSK Liaison to FDA
- Maintains all IND files and databases
- Works closely with: FDA staff, Pharmaceutical Companies, IRB/HRPP, Protocol Review Core (INDC)

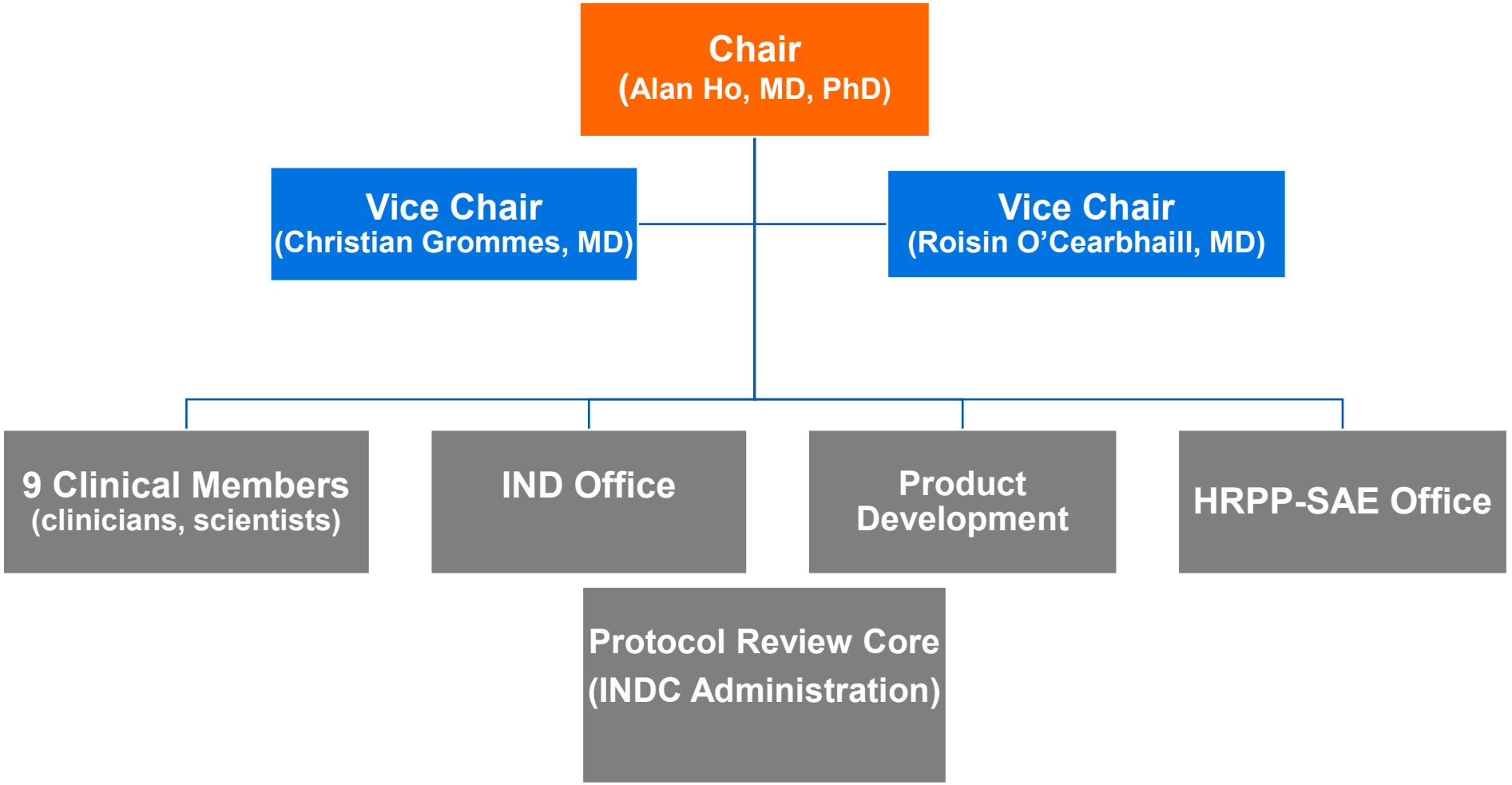
Regulatory Oversight and Product Development Office



Investigational New Drug Committee (INDC) Scope

- All MSK IND/IDE protocols must be reviewed by the INDC prior to FDA submission
- Review IND applications for completeness, accuracy, compliance with published FDA regulations, guidance documents and consistency with other institutional IND's.
- Review annual reports and progress reports for all active MSK held IND/IDE studies
- **NOT required by the FDA and unique to MSK!**

INDC Membership



YOUR TURN!

- IN THE CHAT, can MSK investigators communicate directly with the FDA?
  - Yes
  - No

NO
The IND Office is the liaison between MSK and the FDA

YOUR TURN!

- IN THE CHAT, every institution has an IND Committee?
  - Yes
  - No

NO
An INDC is not required by the FDA and is unique to MSK

IND/IDE Applications at MSK

IND Applications

- Investigator prepares the application
- Types of INDs:
  - New IND application (full application)
  - New protocol under an existing IND application
  - Cross-reference IND application
  - IND exemptions

Full IND Application (New IND)

- An investigational product that has not been approved by the FDA
- MSK is responsible for manufacturing of the investigational product(s)
- **2024 INDC Volume= 2**
- **Example:** A Phase I Study of MB-CART19.1 Cellular Therapy for Relapsed/Refractory Primary and Secondary Central Nervous System Lymphoma (CNSL) Using On-Site Manufacturing with the CliniMACS Prodigy Device (IRB# 25-066)

New Protocol Under Existing IND

- New study using an investigational agent that has an existing MSK held IND
- Separate IND number is not required
- Protocol is added under the IND number that is already active for the investigational agent(s) being used

- **2024 INDC Volume= 2**

- **Example:** 18-F-FMISO, 19-28Z Retrovirus, 68Ga-Labeled PSMA Ligand

Cross-Reference IND Application

- Drug manufacturer:
  - Provides investigational agent(s) and cross-reference letter(s)
  - Does not monitor the trial
  - May receive data per the Clinical Trial Agreement

- Allows the FDA to access data from the drug manufacturer's IND

- MSK responsible for all FDA reporting

- **2024 INDC Volume= 22**

- **Example:** A Phase II Study of Sacituzumab Govitecan in Combination with Cetuximab in Patients with Recurrent Metastatic HNSCC That Has Progressed After First Line Therapy (IRB#25-094)

IND Exemption: FDA Guidance

1. Not intended to support FDA approval
2. Not supporting a change in advertising
3. Does not significantly change risk by change in dose, schedule, route, etc.
4. Conducted under 21CFR parts 56, 60 (informed consent, IRB approval, etc.)
5. Does not charge for or promote investigational drugs

INDC will review request and determine one of the following:

- Designate the trial IND exempt
- Require an IND to be filed
- Submit to the FDA for final determination

2024 INDC Volume= 9

Example: Phase II Trial of Enfortumab Vedotin in Recurrent and/or Metastatic Adenoid Cystic Carcinoma (IRB# 24-215)

What is included in the IND application?

- Form 1571
- Protocol and Informed Consent
- Introductory Statement
- General Investigational Plan
- Form 1572s and CVs
- Investigator's Brochure
- Cross-Reference Letters

- Chemistry, Manufacturing, and Control Data (**New IND**)
- Pharmacology and Toxicology Data (**New IND**)
- Previous human experience (**New IND**)
- Additional Information
- Exemption request memo (**IND Exemption Request**)
- Protection of Human Subjects Form

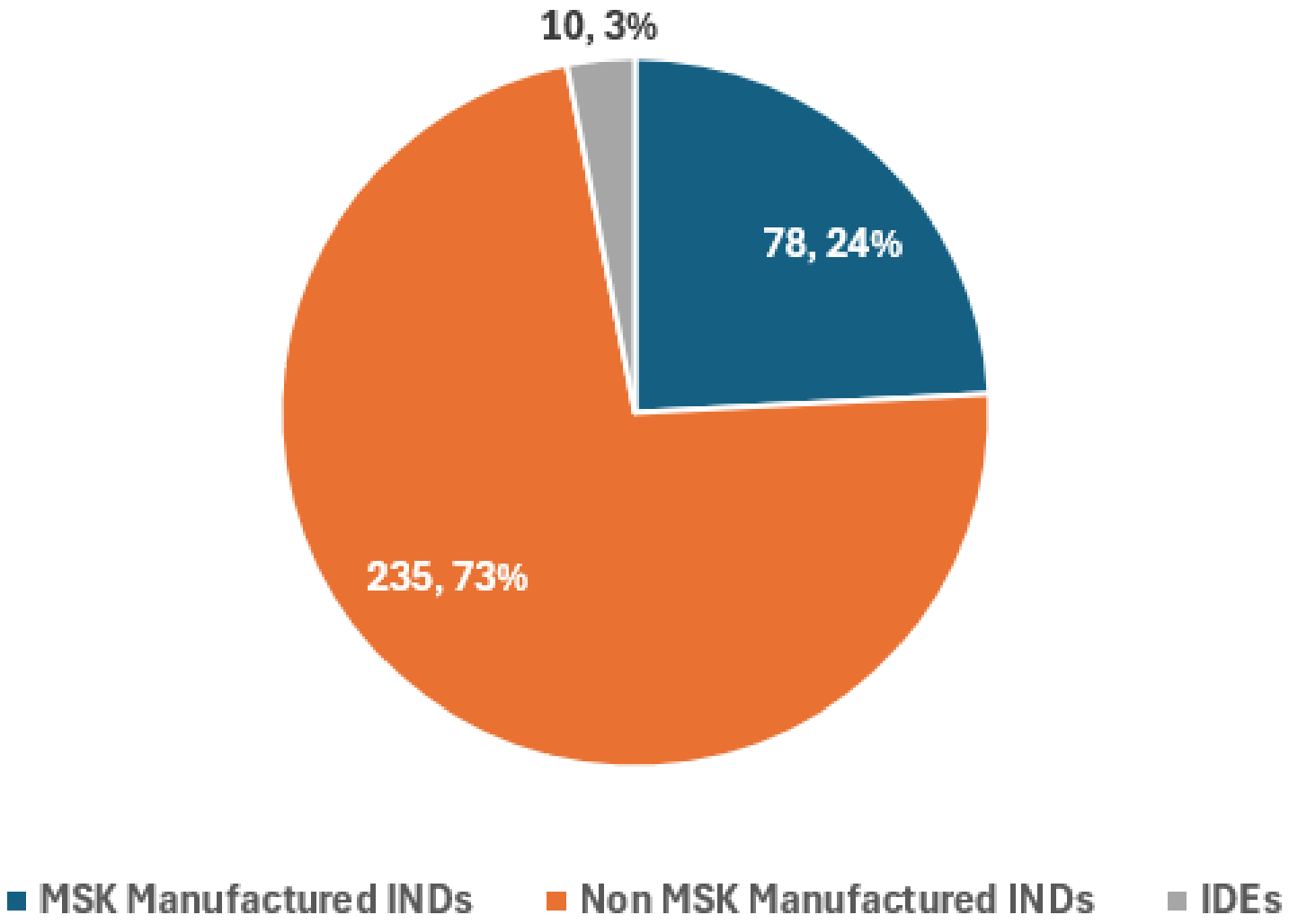
When is an IDE required?

- IDE= Investigational Device Exemption
- Collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket (510k) submission to the FDA
- Risk is determined by the IRB (Non-Significant or Significant)
- Required when opening a study with a significant risk (SR) device
    - Devices that support or sustain human life, substantially important in diagnosing, curing, mitigating or treating disease or in preventing impairment to human health
    - Examples: implants, in vitro diagnostics (assays) used for protocol-based decisions
    - Decision Tree for In Vitro Diagnostics Assays

What is included in the IDE application?

- Cover Letter
- Table of Contents
- Report of Prior Investigations
- Introductory Statement
- General Investigational Plan
- Risk Analysis
- Protocol and Informed Consent
- Form 1572
- Miscellaneous Correlative Documents
- Manufacturing Information
- Photographs

MSK IND Portfolio



YOUR TURN!

- IN THE CHAT, all IND exemption requests must be sent to the FDA
  - Yes
  - No

NO
IND exemption requests are reviewed by the INDC who may defer the application to the FDA for final review

FDA Review & Reporting

FDA Review

- Scientific Discipline Team Leaders notified, and reviewers assigned:
  - Clinical
  - Nonclinical pharmacology/toxicology
  - Chemistry
  - Clinical pharmacology
  - Biostatistics (for Phase 3 protocols)
  - Consult reviewers as needed

- 30 calendar day waiting period- New IND, Cross-Reference, New Protocol to Existing IND

- Letter sent to the INDC Chair (includes assigned #)
  - IND#: drug & botanicals
  - BB-IND#: biologic products
  - IDE #: devices

FDA Review: Clinical Hold

- An order issued by FDA to the sponsor of an IND to delay a proposed clinical investigation or suspend an ongoing clinical investigation.
- Full Clinical Hold: A delay or suspension of the clinical study under an IND.
- Partial Clinical Hold: A delay or suspension of only part of the clinical study under an IND.

FDA Review: Clinical Hold

Why impose a Clinical Hold?

- Exposed to an unreasonable and significant risk of illness or injury
- Clinical investigators are unqualified
- Investigator Brochure is misleading, erroneous, or incomplete
- Insufficient information to assess risks to subjects
- Exclusion by gender for life-threatening disease

IND Annual Report/IDE Progress Report

- Due within 60 days of anniversary date
- Summary information for all studies, including:
  - Safety results, significant changes in product manufacturing, pre-clinical study status
  - General investigational plan for upcoming year
  - Any Investigator Brochure revisions
  - Significant Ph I protocol modifications
  - Significant foreign marketing developments during prior year

- **2024 INDC Annual Report Volume= 252**

YOUR TURN!

- IN THE CHAT, what committee is responsible for determining if a device is significant or non-significant risk?

IRB

YOUR TURN!

- IN THE CHAT, an IND annual report is due within how many days of the anniversary date

60 days

Resources

Important PI Tips to Remember….

- Minimal Submission Requirements:
  - Know your IND Type
  - Ensure relevant pre-clinical testing is completed (New INDs)
  - Confirm IND plan is appropriate with the IND Office
  - Obtain required documents
  - Follow instructions in protocol template
  - Confirm supply source (commercial vs investigational)
- Prepare/Draft IND submission packet
  - Collaborate with various teams (e.g., PAC, Product Development, RMIP Core, MSK Laboratory)
- Resources on the Clinical Research Portal-templates, How Tos, etc.

Resources

- OneMSK Clinical Research Portal: Templates, Instructions, How To Documents: https://mskcc.sharepoint.com/sites/pub-ClinResearch/SitePages/Regulatory-Oversight-and-Product-Development.aspx

- Decision Tree for In Vitro Diagnostics Assays

- FDA Website and Guidance Documents

- IND Office: rtmindo@mskcc.org

- Protocol Review Core/INDC: zzPDL_RTM_CRA_INDC@mskcc.org

Memorial Sloan Kettering
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