

Incorporating Cardio-Oncology in Clinical Trial Design

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Disclaimer

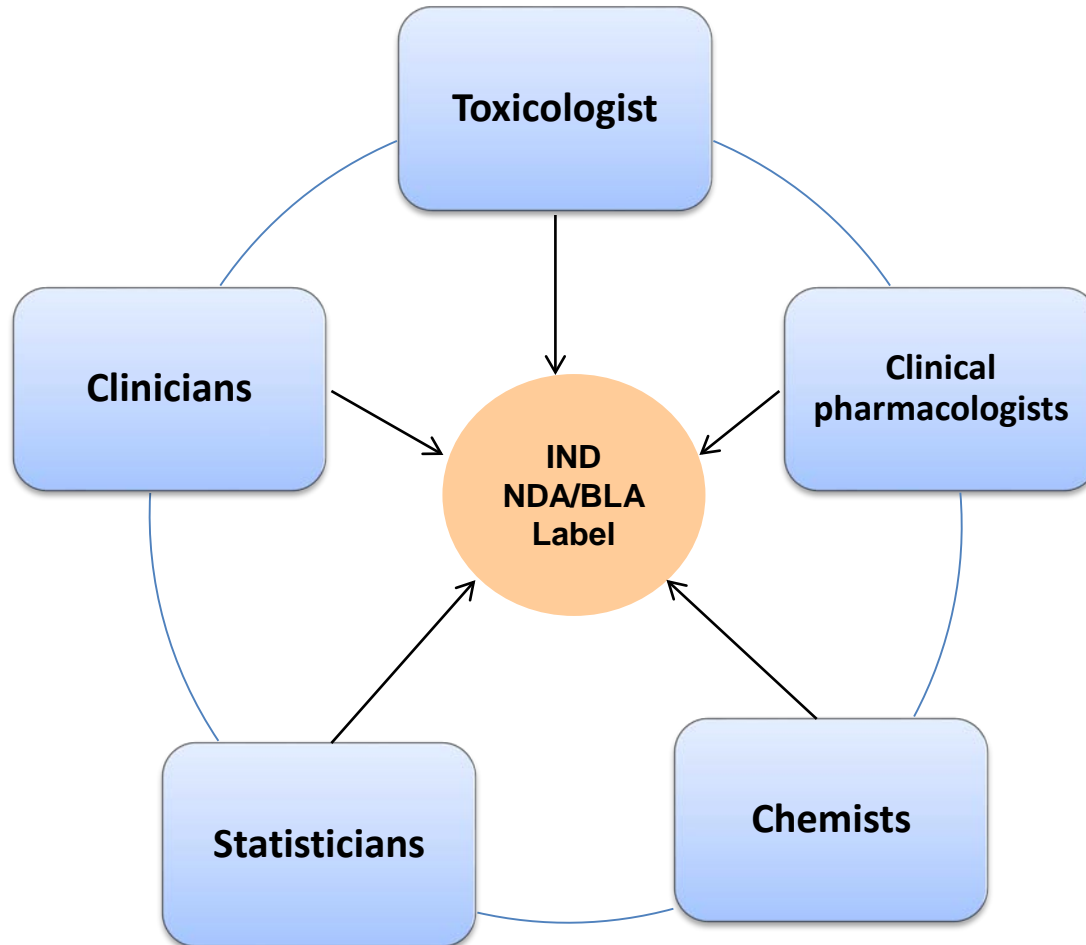
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FDA Mission

- FDA is responsible for:
 1. promote the public health by reviewing clinical research and taking appropriate action on the marketing of regulated products, and
 2. protect the public health by ensuring that human drugs are **safe** and **effective**.

FDA Safety Review: Takes a Village



Identification Of CV Toxicities In Trials Challenging

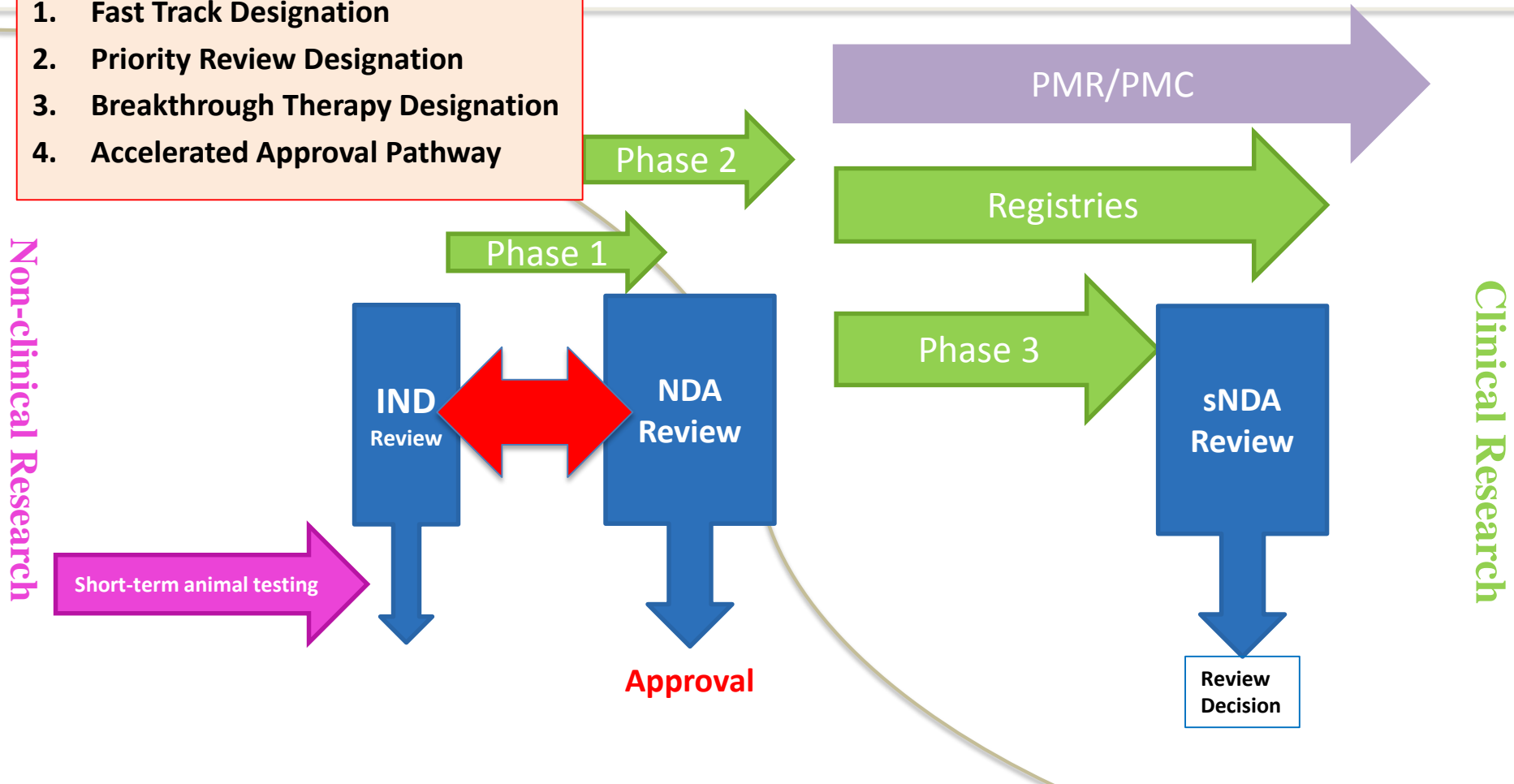
- **CV toxicities rare**
- Trial design issues
 - Cancer trials are small / non-RCT
 - Combination studies with agents with CV toxicities
 - Monitoring elements
- CTCAE
- Under reporting

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Oncology Drug Development

- 1. Fast Track Designation
- 2. Priority Review Designation
- 3. Breakthrough Therapy Designation
- 4. Accelerated Approval Pathway



➤ ↑ # approvals , but ↓ pre-approval safety information

Regulatory Flexibility in Oncology

Safety

- Historically, acceptance of higher degrees of toxicity
- Abbreviated nonclinical studies per S9 guidance



Efficacy

- Acceptance of a Single Trial rather than ≥ 2
- Acceptance of Accelerated Approval Pathway

Overall Risk:Benefit Determination

Takes into consideration more than just the safety and efficacy data: Available Therapy, Disease, Indication, Regulatory Precedence, State of Science

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Monitoring an Adverse Event

- Different from reporting an adverse event
- Prospective
- Standard assessment
- Protocol specific instruction

- Recognition of ADR versus adverse event
 - based on clinical judgment vs algorithm

➤ Incorporating Cardio-oncology in Trial Design

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Is CTCAE Optimal for CV Safety Reporting?



- How to improve CV toxicities data collection and reporting within cancer trials ?
- **Adjudication ?**

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

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Assessment of Causality

- Presence of multiple risk factors
 - Patient’s baseline risk factors (age)
 - Previous exposure to cardiotoxic agent(s)
 - Some tumors may directly affect the CV system (myeloma)
 - Combination studies with agents with CV toxicities

➤ Incorporating Cardio-oncology

Elements of Safety Review

- Before approval

- Non-clinical toxicology
- Prior experience with the drug or class
- Clinical safety review
 - Pooled database; early studies and Randomized data
 - DLTs, MTD, RP2D, All grades AEs, SAE, Grade 3,4,5
 - Drop outs and discontinuations
 - Dose modifications & interruptions
 - Drug exposure; time and dose dependency of AEs
 - Drug-disease and drug-demographic interactions

- Post approval

- Post marketing safety reports
- REMS
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program
- Post marketing trials and observational studies (including PMRs)
- Reports, Literature

FDA Sources of Postmarket Reports



Patients, consumer, and healthcare professionals

Voluntary

Voluntary

FDA MedWatch

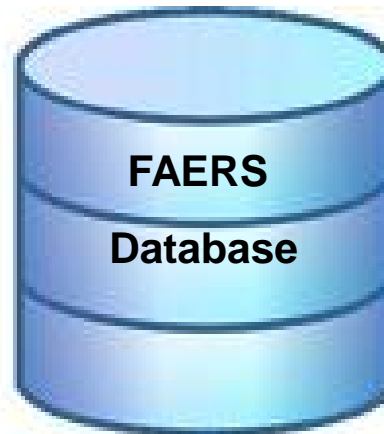
Manufacturer

Food and Drug Administration

MEDWATCH

Regulatory Requirements

FDA



5% of all reports

95% of all reports



Challenges of Evaluating Postmarket Reports of Other Cardiovascular Toxicity

- Differentiating other cardiovascular adverse events from the spectrum of myocarditis
- Reported cardiovascular adverse events have a high background rate in the general population
- Potential contributory role of comorbidities or concomitant medications
- Variable quality of reporting

FDA Efforts to Improve Awareness, Monitoring and Management of CV Toxicity



- Educational sessions at meetings
- FDA Cardio-oncology Workshops
- Working Groups
- Collaborative Research



Future Directions/Implications

- Cardiac monitoring on oncology trials
- Continued pharmacovigilance monitoring
- Determine optimal language in the product labeling to convey risk to health care practitioners
- Algorithms for diagnosis, monitoring and treatment
- Research questions: Underlying mechanism, risk factors
- Collaborative work with cardiologists, oncologists, and industry

Eligibility Criteria-Organ Dysfunction Working Group Recommendations

- Baseline clinical evaluation and use of ECG monitoring in early-phase studies to assess QTc Prolongation need to be in coordination with regulatory agencies, especially in early-phase studies.
- Inclusion of patients with cardiovascular dysfunction may be possible when the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of these patients is safe.
- Ejection Fraction values should not be used in isolation to exclude patients from trials. Trials should recommend investigator assessment of a potential participant's risk for heart failure with a validated clinical classification system (e.g., the New York Heart Association Functional Classification).



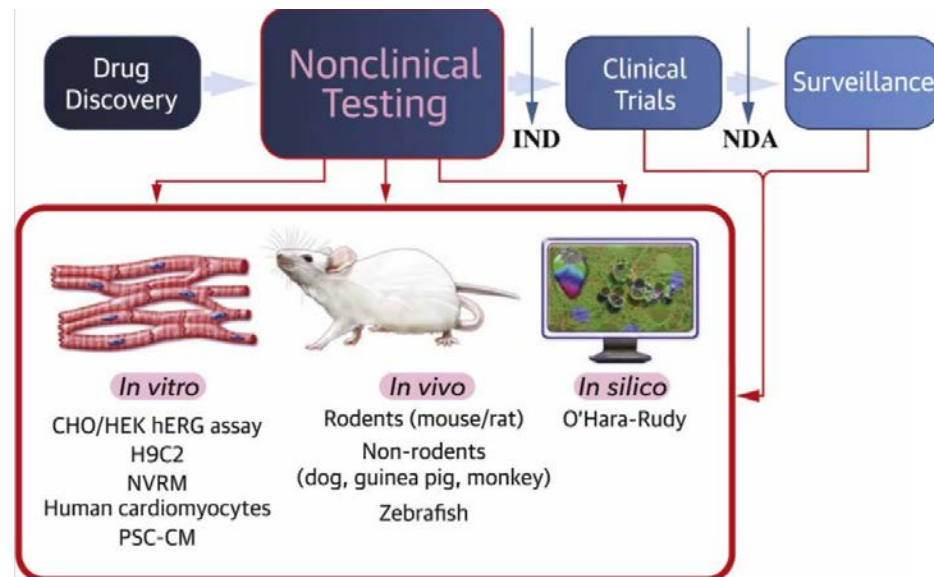
Eligibility Criteria-Organ Dysfunction Working Group Recommendations

- In oncology trials, cardiovascular safety measures and close collaboration with cardiology should be considered, particularly when investigating compounds or regimens where trial-emergent cardiac toxicity is a factor.
- Treatment-emergent cardiac adverse events may be difficult to predict and assessing the causality is generally challenging.
- Capturing patients' baseline cardiovascular risks, can assist in the assessment of the causality of the cardiovascular adverse events (e.g. ischemic versus drug-related).

Incorporating Cardio-oncology Into Cancer Drug Development

- Goal: effectively and efficiently provide clinically and scientifically meaningful data.

Cardio-Oncology Research



Thank you!



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