Regulatory Considerations for Use of New Approach Methodologies (NAMs) for Cardiovascular Drug Products

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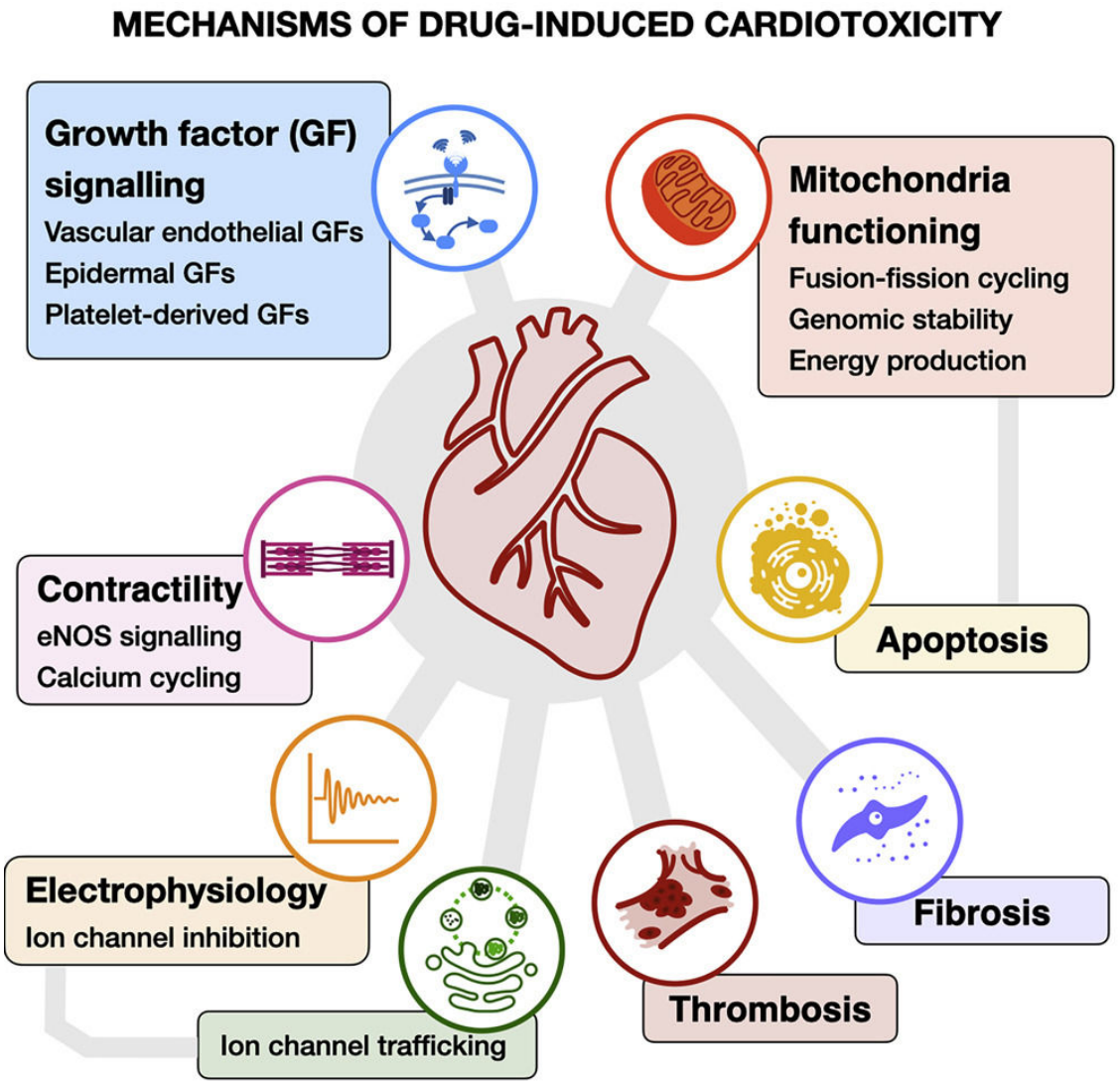
The views expressed in this presentation are the opinion and experience of the individual presenter and are not to be construed as formal FDA recommendations. Where possible, references to formal FDA guidance documents have been provided.

No Disclosures

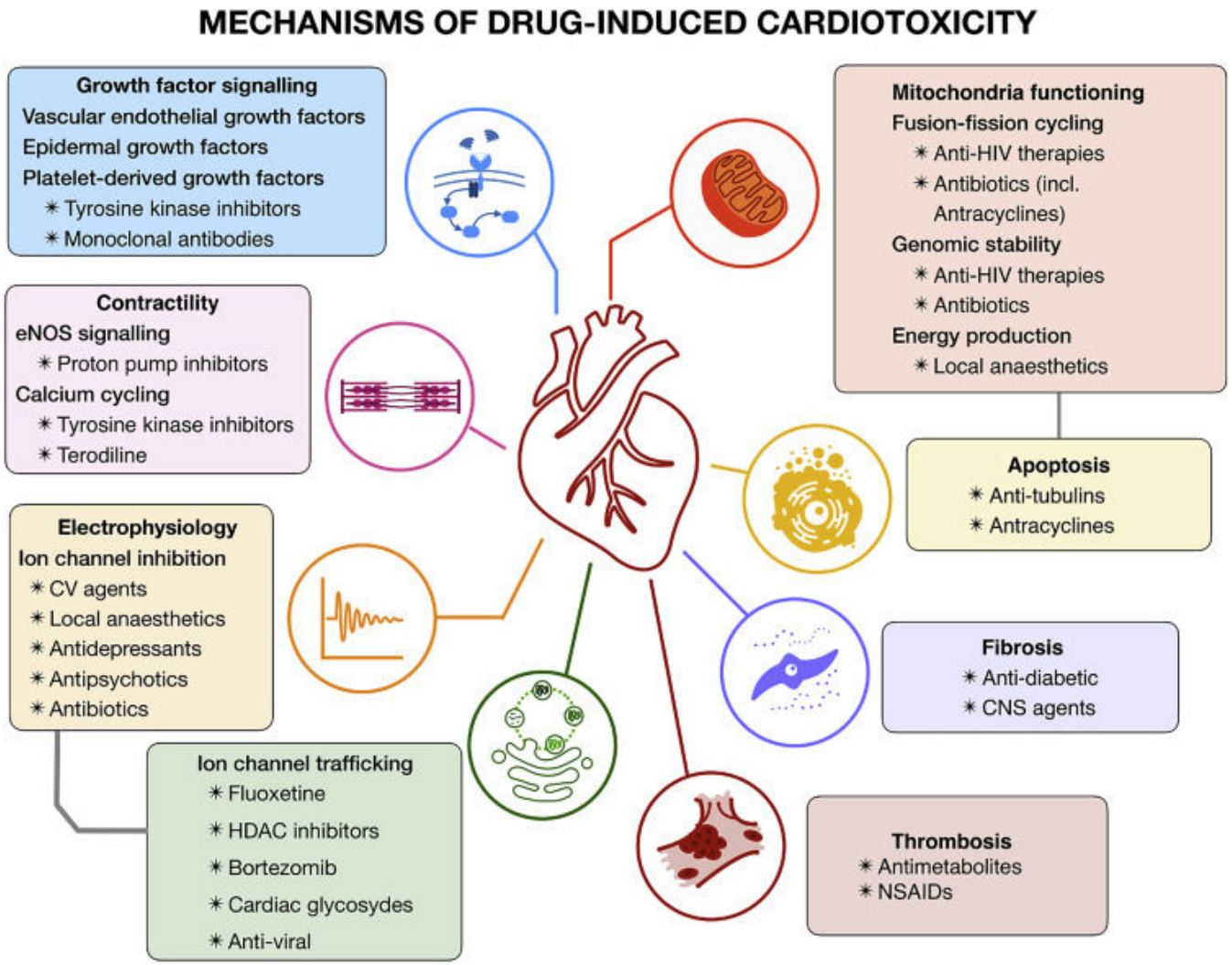
CLINICAL REVIEWER PERSPECTIVE

CARDIOTOXICITY: *Diverse Effects*



Mamoshina et. al., (2021): https://doi.org/10.1016/j.xcrm.2021.100216

CARDIOTOXICITY: *Diverse Drugs*



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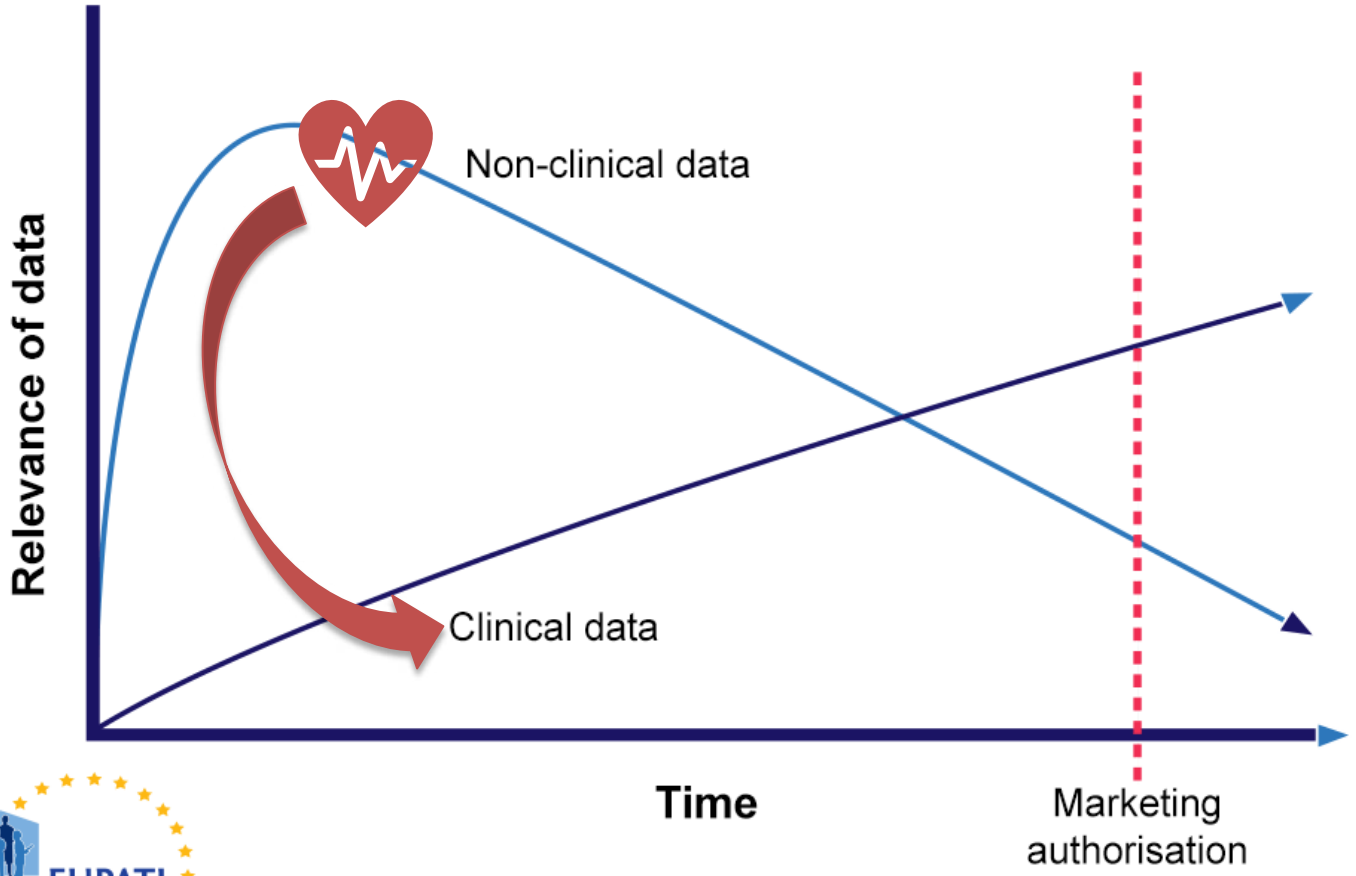
Drug Development: *CV Safety*



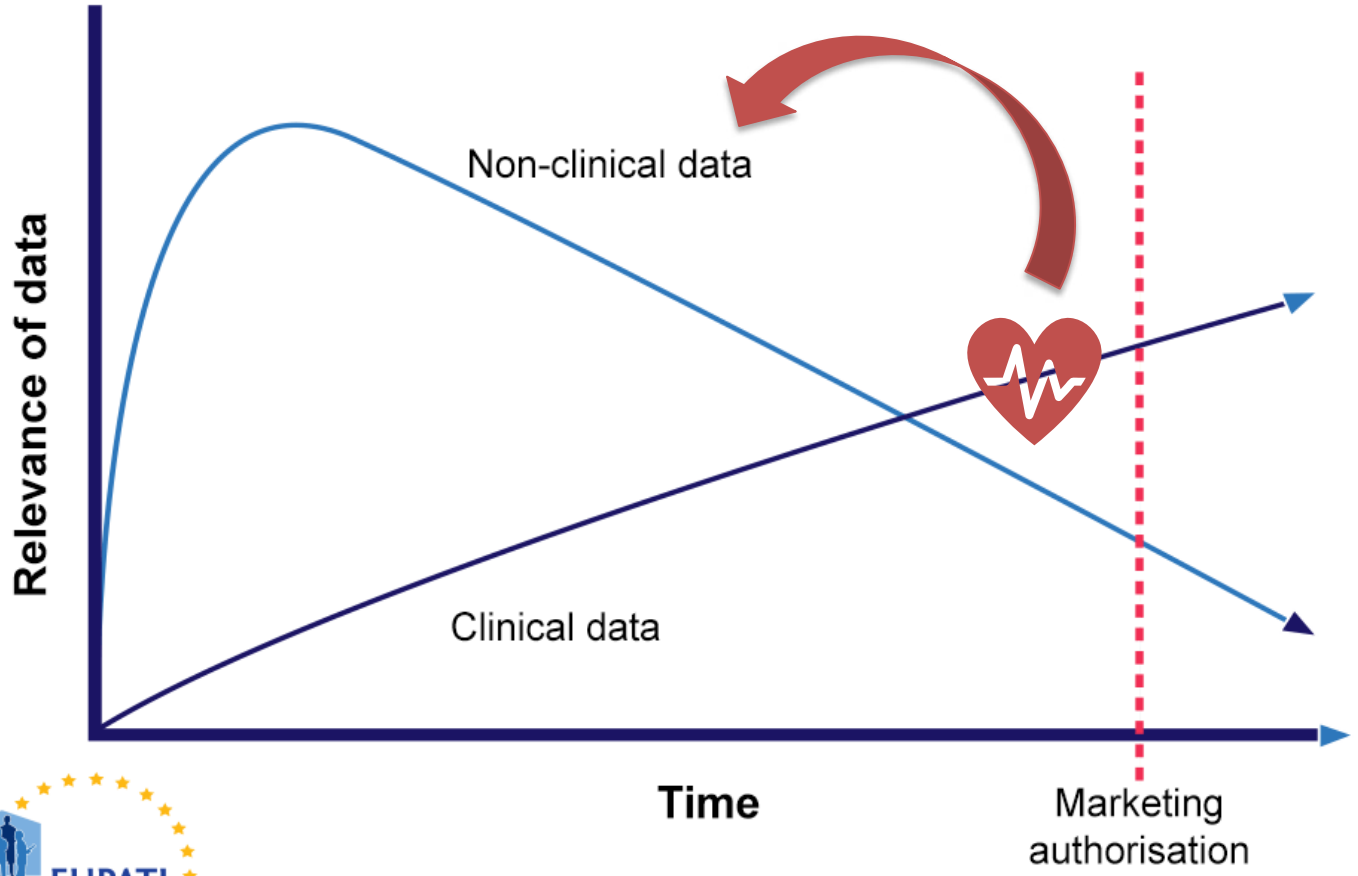
EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Adapted from Nieto-Guiterrez, M. (2011) *Non-clinical assessment requirements.* London: European Medicines Agency.

Preclinical Stages: *baseline risk assessment*

Clinical Stages: *chronic risk assessment // de-risking observed cardiotoxicity*

Drug Development: *CV Safety*



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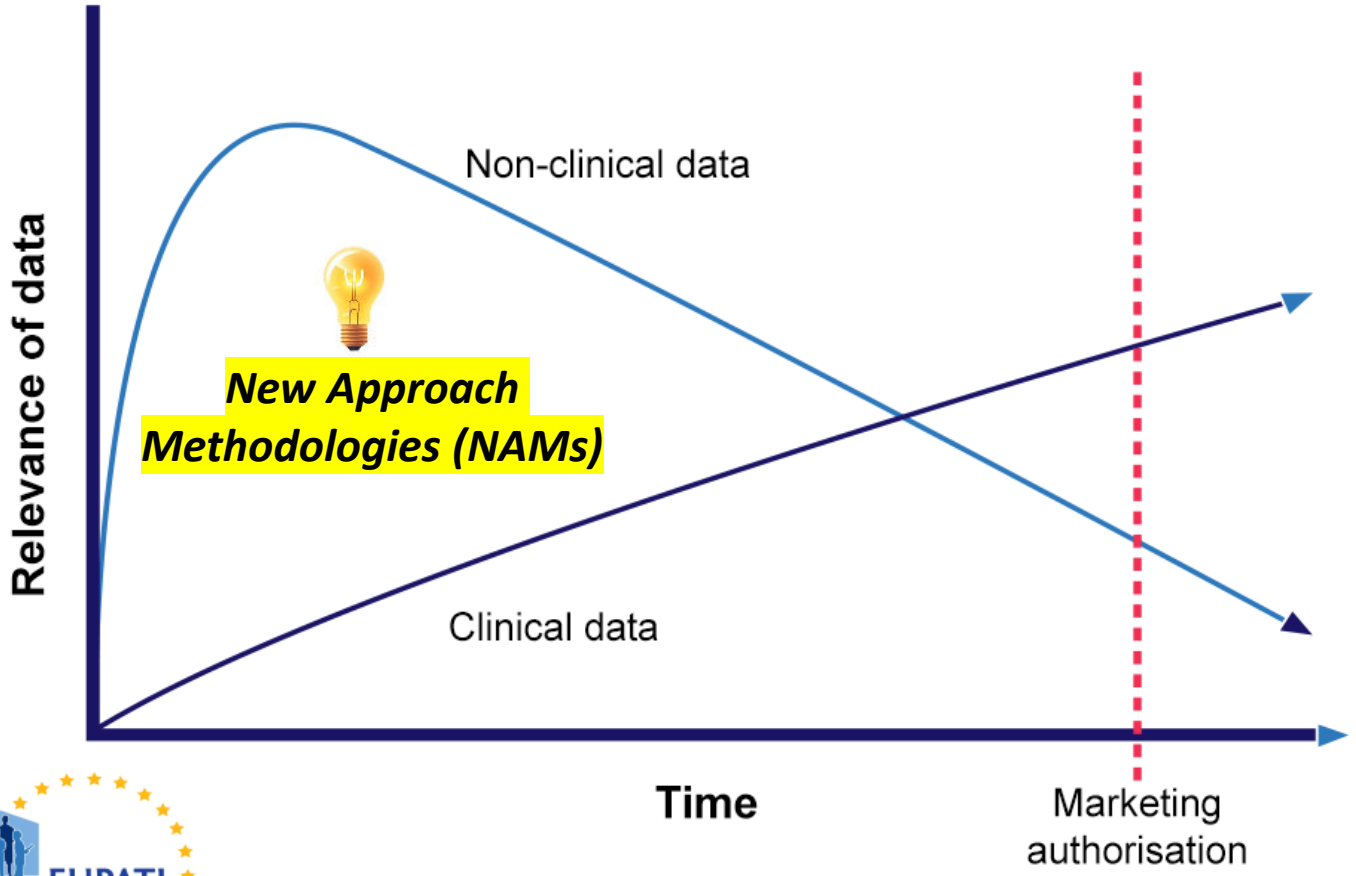

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REGULATIONS & GUIDANCES

Regulations: *CV Safety*

Regulations

- **21 CFR 314.50:** Content and format of an NDA

  (d)(2) Nonclinical pharmacology and toxicology section

  (ii) Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use

- **21 CFR 601.2:** Applications for biologics licenses; procedures for filing
  - *(a) shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency;*

ICH Guidance: *S7A*

Guidance for Industry

S7A Safety Pharmacology Studies for Human Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

ICH
July 2001

This guidance was developed to help protect clinical trial participants and patients receiving marketed products from potential adverse effects of pharmaceuticals, while avoiding unnecessary use of animals and other resources.

ICH Guidance: *S7B*

Guidance for Industry

S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2005
ICH

This guidance describes a nonclinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization. The guidance includes information concerning nonclinical assays and integrated risk assessments. The assessment of the effects of pharmaceuticals on ventricular repolarization and proarrhythmic risk is the subject of active investigation.

ICH Guidance: *M3(R2)*

Guidance for Industry

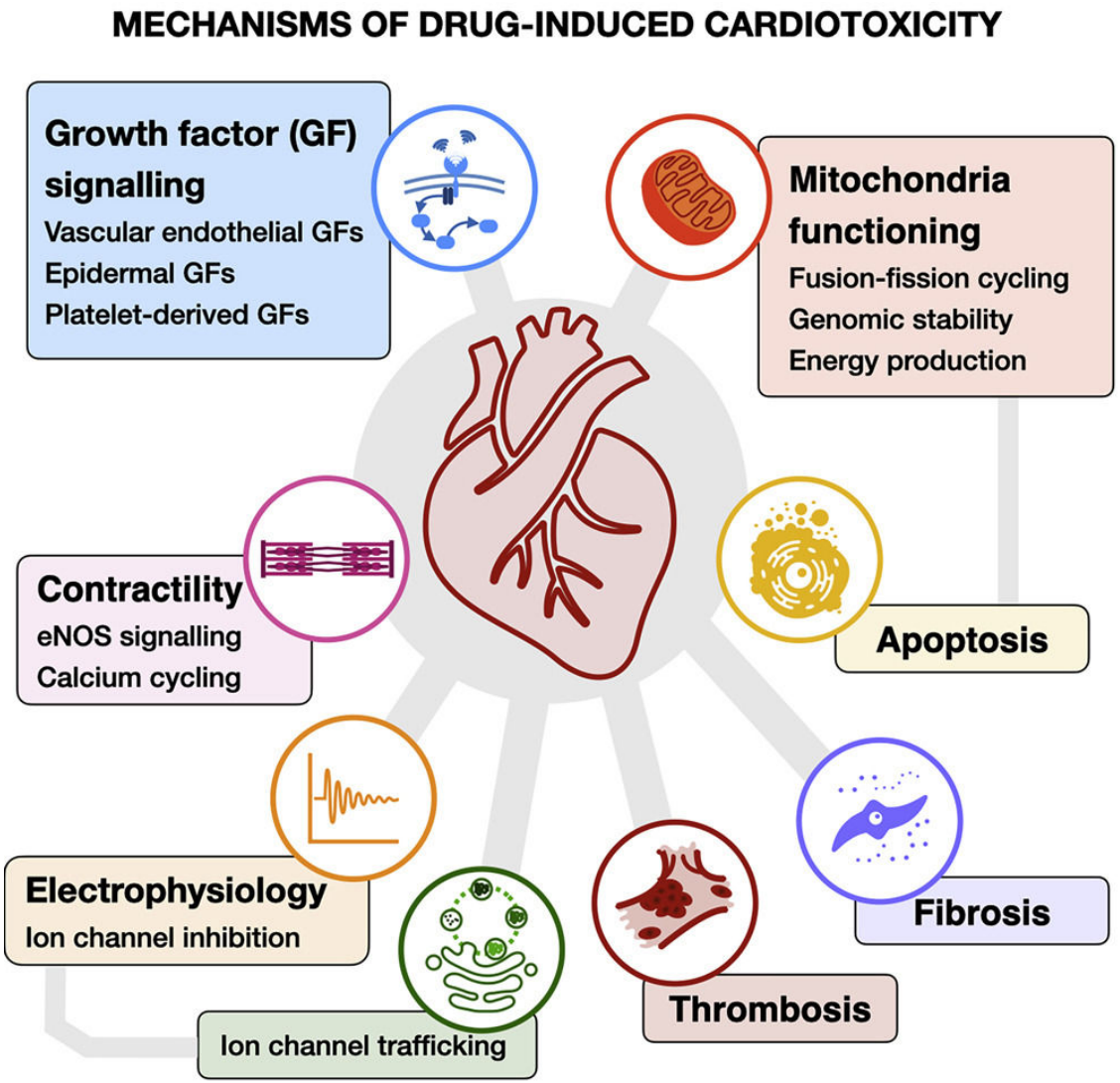
M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Drug Evaluation and Research (CBER)

January 2010
ICH

The purpose of this document is to recommend international standards for, and promote harmonization of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals. Harmonization of the guidance for nonclinical safety studies will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions.

CARDIOTOXICITY: *Diverse Effects*



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Challenges & Questions

Can NAMs replace the full spectrum of preclinical CV toxicity testing required by regulations & guidance??

RECENT FDA EFFORTS: *NAMs*

Roadmap to Reducing Animal Testing in Preclinical Safety Studies

- Announced April 10, 2025

- FDA tasked with accelerating validation and adoption of human-relevant New Approach Methodologies (NAMs) including:

  - **3R** principles of **R**educing, **R**efining, and **R**eplacing animal testing
  - In vitro human-derived systems (organoids, microphysiological mystems [MPS] or complex in vitro models [CIVM]) *e.g., engineered cardiac tissues*
  - ***In silico tools and computational modeling***
  - Other innovative platforms

- **Long-term Goal (3-5 years):** FDA aims to make animal studies the exception for pre-clinical safety/toxicity testing of monoclonal antibodies (mAb) and then eventually all drugs/therapeutics

GUIDANCE DOCUMENT

Monoclonal Antibodies: Streamlined Nonclinical Safety Studies

Draft Guidance for Industry

DECEMBER 2025

Download the Draft Guidance Document | Read the Federal Register Notice

Draft

Not for implementation. Contains non-binding recommendations.

This guidance is being distributed for comment purposes only.

[Monoclonal Antibodies: Streamlined Nonclinical Safety Studies | FDA]

Recent FDA Perspective Article: *NAMs*

Published in final edited form as:
Int J Toxicol. ; : 10915818251384270. doi:10.1177/10915818251384270.

FDA/CDER/OND Experience With New Approach Methodologies (NAMs)

Jia Yao, PhD[1], Jackye Peretz, PhD[1], Ilona Bebenek, PhD[1], Amy Avila, PhD[1], Tessie Alapatt, PhD[1], Bo Lee, PhD[1], Dakshesh Patel, PhD[1], Paul Brown, PhD[1], Karen Davis-Bruno, PhD[1]
[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

FDA/CDER/OND Experience With New Approach Methodologies (NAMs) - PubMed

Comprehensive in Vitro Pro-arrhythmia Assay: *CiPA*

- This initiative involved collaboration among international regulatory agencies, academia, and the pharmaceutical industry, emphasizing the development of nonclinical assays that utilize human-derived cardiac myocytes and advanced computational models to predict proarrhythmic risk more accurately.

- The CiPA framework is structured around four main components: ion channel studies, ***in silico modeling***, stem cell-derived myocyte evaluations, and clinical electrocardiogram (ECG) assessments.

The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative — Update on progress - ScienceDirect

NAM Qualification

- Roadmap to Reducing Animal Testing in Preclinical Safety Studies:
  - Encourage and support targeted development of human relevant NAMs
  - Establish validation and qualification pathways for NAMs

- FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program
  - Specific DDT qualification program supporting development of NAMs
  - Qualified NAMs can be relied upon to have a specific interpretation and application in drug development and regulatory review *within its stated COU*.
  - Includes CVIM/MPS incorporating hiPSC-CMs
  - ***In Silico NAMs??***

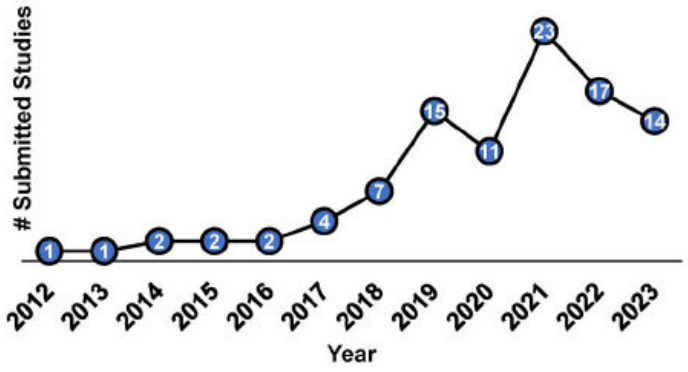
- Other opportunities to engage with CDER to discuss NAMs:
  - PIND/IND Meetings
  - **Collaborative Workshops/Forums!!**

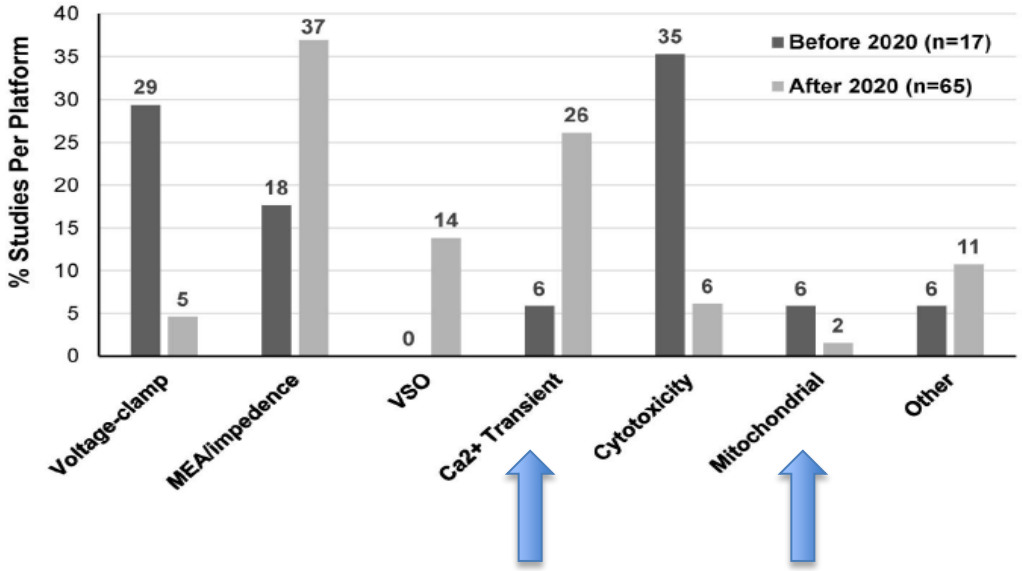
NAM Qualification: *Required?*

NO

CDER IND/NDA Applications: *hiPSC-CMs*

- Number of hiPSC-CM studies submitted to CDER have steadily increased over the past decade*
- Most submitted to FDA with IND opening + often to support electrophysiology findings





Other non-EP mechanisms of CV Tox

https://doi.org/10.1093/toxsci/kfaf064

CONCLUSIONS

- Most nonclinical data is received prior to FIH dosing and is not sufficient to cover all mechanisms of drug-induced toxicities
  - Current lack of nonclinical assays for mechanistic understanding of CV toxicity other than electrophysiology; ***in silico NAMS?***
- FDA's Roadmap to Reducing Animal Testing in Preclinical Safety Studies includes a strategy to validate and adopt human-relevant NAMS to streamline drug development and reduce animal use
  - *First Draft Guidance for Industry on Monocolonal Antibodies (Dec 2025)*
- Development of human stem-cell based MPS/CIVM have the potential to address current nonclinical CV testing deficiencies while reducing or replacing the need for animal testing
- Development of ***in silico NAMs*** may further complement other modalities to improve understanding, prediction, and de-risking of CV toxicity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