



Non-Clinical Cardiovascular Safety Testing: Moving Forward

Douglas C. Throckmorton, MD
Deputy Director for Regulatory Programs
CDER, FDA

Safety Pharmacology Society Webinar
January 2015

Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

Outline

- **Need for Efficient Drug Development**
- **Challenge of Cardiovascular Toxicity in Drug Development**
- **Promise and Challenge of Using Non-Clinical Models to Replace Clinical Testing**

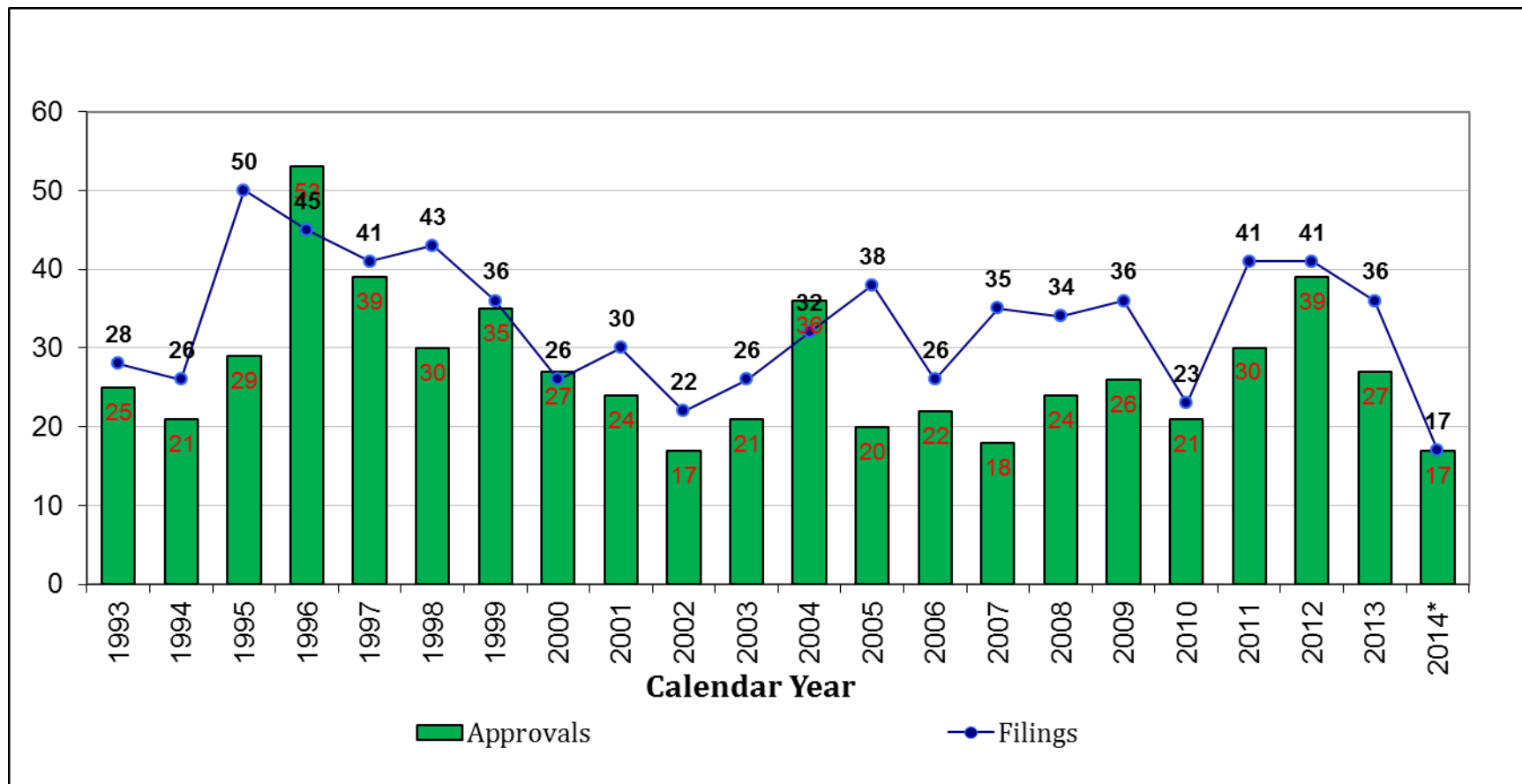
Central Messages

- Needed optimization of drug development requires:
 - Broad stakeholder interaction between regulators, academics and industry
 - Ongoing willingness to test our current testing paradigms and look for more efficient approaches without lowering our standards for safety
 - Non-clinical cardiovascular safety testing is an important and promising area of focus for FDA



Challenge of Efficient Drug Development

CDER NME NDAs/BLAs† Filings and Approvals



Data as of 6/30/2014

† Multiple applications pertaining to a single new molecular/biologic entity (e.g. single ingredient and combinations) are only counted once. Therefore, the numbers represented here for CY14 filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded

* Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year. Certain applications are within their 60-day filing review period and may not be filed upon completion of the review.



Challenge of Cardiac Toxicity in Drug Development



Table I. Leading reasons for drug withdrawal over the last 40 years^{1,2}

Worldwide withdrawal (121 compounds)		US Withdrawal (95 compounds)	
Reason	Percent	Reason	Percent
Hepatotoxicity	26	Cardiovascular safety (proarrhythmia)	19 (12)
Hematologic toxicity	10	Neuropsychiatric effects	12
Cardiovascular safety	9	Hepatotoxicity	9
Dermatologic effects	6	Bone marrow toxicity	7
Carcinogenicity	6	Allergic reactions	6

Challenge: Identifying Common CV Toxicities

QT-Interval Prolongation and
Torsade de Pointes (TdP)



Drugs Removed From Market for Arrhythmia Risk

- **Encainide (Enkaid[®])** **1991 (1986)***
- **Terfenadine (Seldane[®])** **1998 (1985)**
- **Astemizole (Hismanal[®])** **1999 (1988)**
- **Grepafloxacin (Raxar[®])** **1999 (1997)**
- **Cisapride (Propulsid[®])** **2000 (1993)**
- **Levomethadyl (Orlaam[®])** **2003 (1993)**

* year of removal (year of approval)

Responses to Drug-induced TdP

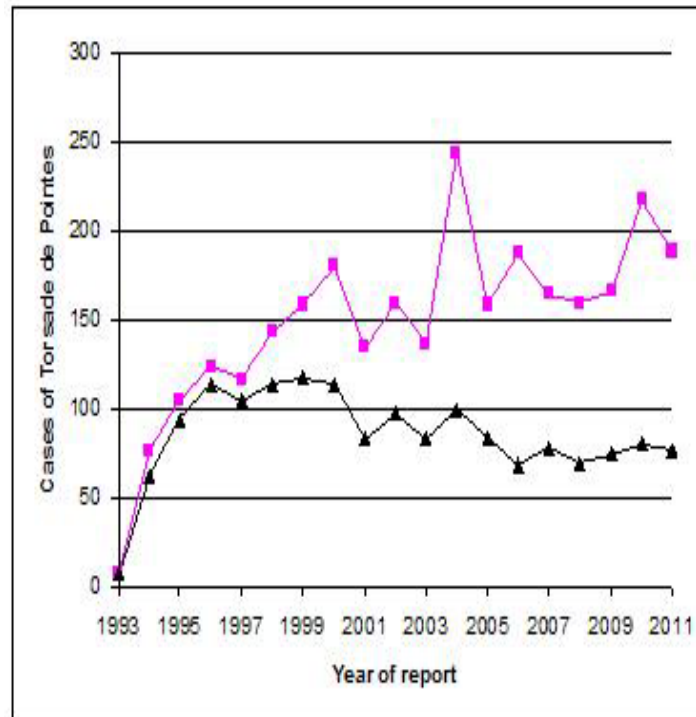
- **Regulatory**
 - ICH S7B, E14 guidances
 - FDA QT interdisciplinary review team
- **Technical**
 - HL7 ECG data standard
 - ECG Warehouse
- **Community & Research**
 - Specialized QT study vendors
 - ECG Metrics Consortium
 - Cardiac Safety Research Consortium

Direct costs

- Since 2005
 - Around 300 Through QT ('TQT') studies reported to FDA
 - Estimated 450 TQT studies performed
 - Estimated cost per study is few million dollars
- Total of ~\$1B over 9 years

Impact

- **No new drug withdrawals**
 - Decline in TdP as a reported adverse event
- **Negative impact on drug development?**



All drugs

Excluding anti-arrhythmic

Challenge: Identifying Common CV Toxicities

Other Unanticipated CV Toxicities

Other Reported Drug-Induced Cardiovascular Toxicity

- Tyrosine Kinase Inhibitor* cardio-toxicity:
 - Reduced myocardial contractility, CHF
 - Hypertension
 - QT prolongation
- Antibody pro-thrombotic effects
 - Bevacizimab, Ponatinib

*--imatinib mesylate, dasatinib, nilotinib, sunitinib, sorafenib and lapatinib

Challenge: Efficient Development

- Identify safety signals early and accurately wherever possible
- Monitor for unanticipated or incompletely characterized cardiovascular toxicities after approval
- Additional important goal: reduce, replace and refine use of animals



Meeting These Challenges: Role of Non-Clinical Testing

Goals of Nonclinical Test Development

- One goal is to replace clinical testing
 - When that's not possible, non-clinical testing has a role in understanding mechanisms, reducing clinical testing and mitigating toxicities
- Efficient use of animal resources is separate important goal: can we be smarter about collecting nonclinical data?
 - e.g., collection of parts of S7a/b as a part of other non-clinical studies

QT as an Example: Changing the Paradigm

- E14 and S7B have allowed us to avoid additional drug withdrawals
 - Clinical testing paradigm (TQT studies) carries additional cost in \$\$ and time
- Question to be addressed: can improved science provide alternative to TQT?

Reasons for Optimism

- Basis for TdP is mechanistically well-understood and testable
- Technology exists to be able to test drug effects on isolated channels using high-throughput technology that is reasonably available
- Computational techniques exist to analyze data and model effects on proarrhythmic risk
- Group has committed resources and time to testing a new assay system to try to assess clinical CV risk using comprehensive in vitro test system

Challenges in Applying this Model in Other Areas of CV Safety

- Identification of appropriate model
 - Off-target toxicities frequently not well-understood mechanistically (e.g., TKI inhibitors)
 - Models vary in their test characteristics in ways that are sometimes hard to predict (e.g., dog versus primate)
- Rigorous assessment of predictive power of model and testing strategy necessary
 - Assay sensitivity (e.g., telemeterized animals vs cageside observations for CV effects)

Challenges in Applying this Model in Other Areas of CV Safety (cont)

- Toxicities that emerge with chronic exposure challenging to identify in short-term and in vitro models
- Need to identify and use tests that enhance and not impede drug development
 - Consider unintended consequences of new, including new 'add-on' testing

Summary

- Non-clinical testing to identify cardiovascular toxicity is important in drug development:
 - Identifying the toxicity early allows the sponsor to develop ways to prevent or mitigate a toxicity, or abandon a compound early
 - Characterizing toxicities identified late in development or during postmarketing
 - Replacing, refining or reducing human (animal) testing
- Ongoing work to replace clinical testing with in vitro testing for QT interval prolongation provides a possible pathway for other cardiovascular toxicities
 - Collaboration of willing and interested groups is essential
- We have a shared goal of developing efficient testing methods and strategies using non-clinical testing methods to further needed drug development