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Validation and Qualification of New In Vitro Tools and Models for the Pre-Clinical Drug Discovery Process

An FDA Point of View

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Third AIMBE/NIH Workshop on Validation and Qualification of New In Vitro Tools and Models for the Pre-clinical Drug Discovery Process

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Disclaimer

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Outline

- Role of nonclinical studies in drug discovery and development
- Challenges in predicting human outcomes using data from model in vitro systems
- Drug development tools: qualification and context of use
- Discussion

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ROLE OF NONCLINICAL STUDIES IN DRUG DEVELOPMENT

CDER Mission

- The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective.
- CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness.
- It is the responsibility of the company seeking to market a drug to test it and submit evidence that it is safe and effective.

Source: www.fda.gov

Pharm/Tox Testing in Drug Discovery

- Not governed by specific regulatory requirements
- Used to inform the sponsor's decision to select a particular drug candidate for development
  - "Are you feeling lucky?"
- Will be company/product specific, based on:
  - Pharmacologic target
  - Chemical features
  - Current knowledge (institutional, public)
- May incorporate traditional and new technologies:
  - ___omics
  - In silico (chemistry, biology)
  - In vitro (cell lines, iPSC, 2D-3D organ systems)
  - Animal models

Preclinical Pharmacology Studies in Drug Development

- Efficacy *in vitro* and *in vivo* from nonclinical studies may not reliably predict clinical efficacy
  - Heterogeneity of disease
  - Interspecies differences in ADME
  - Role of immune system, etc.
- Preclinical pharmacology studies may be useful for:
  - Suggesting a reasonable mechanism of action
  - Assessing an appropriate dosing schedule
  - Justifying drug combinations
  - Understanding effects at the molecular target (specificity)
  - Identifying and evaluating biomarker performance

..but are generally considered to be of low relevance in making regulatory decisions on efficacy

Adapted from: www.fda.gov/ohrms/dockets/.../2006-4203-S1-02-FDA-Leighton.ppt

Preclinical Toxicity Studies in Drug Development

- Before human studies can begin, an IND must be submitted containing information on any risks anticipated under the conditions of the proposed clinical trials based on the results of pharmacologic and toxicological studies (21 CFR 312.23(a)(8)).

- These preclinical studies are designed to:
  - Permit the selection of a safe starting dose in humans
  - Gain an understanding of target organ toxicity and potential reversibility
  - Estimate the margin of safety between a clinical and a toxic dose
  - Predict pharmacokinetic and pharmacodynamic parameters

References: Preclinical studies for small molecules: ICH M3
Preclinical studies for biologics: ICH S6

Preclinical Toxicity Studies (ICH M3)

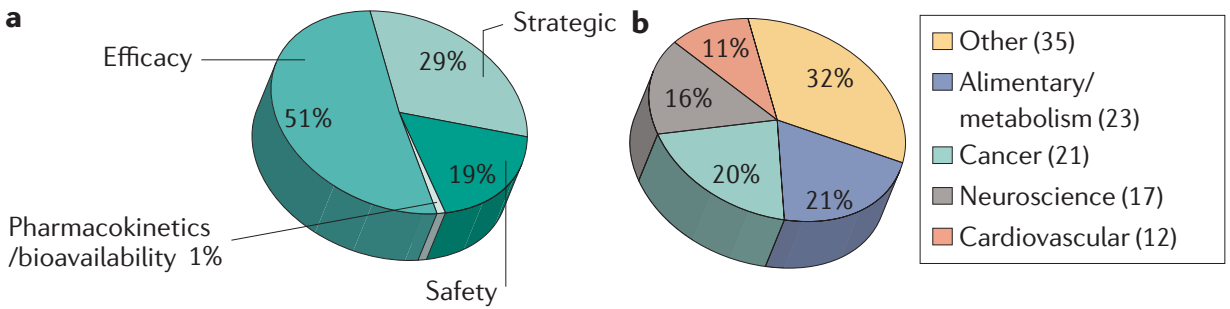
- Safety pharmacology (ICH S7A,B)
  - Cardiovascular
  - Central nervous system
  - Respiratory

  Supplemental (e.g. immunotoxicity: ICH S8)
- Toxicokinetics/pharmacokinetics (ICH S3A – S3B)
- Acute toxicity studies
- Repeated dose toxicity
- Genotoxicity (ICH S2)
- Carcinogenicity
- Reproductive toxicity (ICH S5)

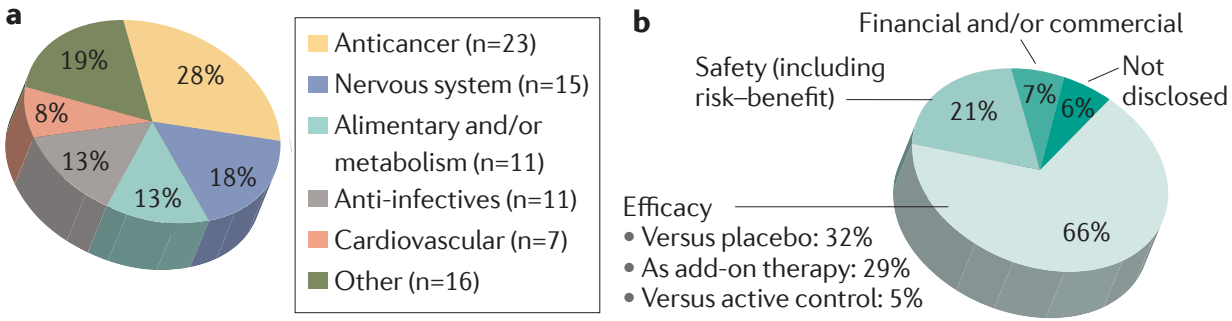
Preclinical TK Studies (ICH S3A)

- To describe the systemic exposure levels achieved by dose and study time course
- To relate exposure to toxicology findings
- To support selection of species and dose regimen for nonclinical toxicity studies
- To support design of additional studies
- Measurements:
  - [D], AUC, C_{max}, [D] = f(t)
  - Parent - metabolite(s)
  - Blood - tissue

Attrition During Drug Development



Phase II failures: 2008-2010. The 108 failures are divided according to reason for failure when reported (87 drugs) (a) and therapeutic area (b).



Phase III and submission failures: 2007-2010. The 83 failures are divided according to therapeutic area (a) and reason for failure (b).

- Phase II failures due to safety = 19% vs. 51% efficacy
- Phase III failures due to safety = 21% vs. 66% efficacy

J Arrowsmith (2011) Nature Reviews Drug Discovery

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Attrition During Drug Development

Phase	Preclinical		Phase I-III		Post-Approval
Information	**Attrition**	**Attrition**	**Attrition**	**Attrition**	**Withdrawal**
Source:	ABPI(2008)	Car (2006)	ABPI(2000)	Olson et al (2000)	Stevens & Baker (2008)
Sample size:	156 CDs stopped	88 CDs stopped	63 CDs stopped	82 CDs stopped	47 drugs
Cardiovascular	24%	27%	35%	21%	45%
Liver	15%	8%	29%	21%	32%
Hematology	3%	7%	3%	4%	9%
Neuro	12%	14%	2%	21%	2%
Immuno	7%	7%	10%	11%	2%
GI	5%	3%	2%	5%	2%
Reproductive	9%	13%	5%	1%	2%
Musculo-Skeletal	8%	4%	5%	1%	2%
Respiratory	1%	2%	2%	0%	2%
Renal	6%	2%	5%	9%	0%
Genetic tox	5%	5%	0%	0%	0%
Carcinogenicity	0%	3%	3%	0%	0%
Other	4%	0%	2%	4%	1%

Adapted from Redfern et al (2010) and provided by Tim Hammond (AstraZeneca)

Challenges in Preclinical Safety Studies

- Typically conducted in healthy animals
- Generally measure "average" drug behaviors in relatively homogeneous test systems
- Focused on robust, dose-dependent toxicity signals
- Designed to characterize the possibility/type of toxicity rather than expected clinical prevalence/magnitude
  - Rodent (to identify life threatening dose)
  - Non-rodent (to confirm non-life threatening dose)
- May not predict human response:
  - Confounding species differences in (e.g.) physiology, ADME?
  - False positive toxicities → no corollary in humans
  - Unlikely to predict rare, idiosyncratic AEs

Not all patients are the same….

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CHALLENGES IN PREDICTING HUMAN OUTCOMES USING DATA FROM MODEL IN VITRO SYSTEMS

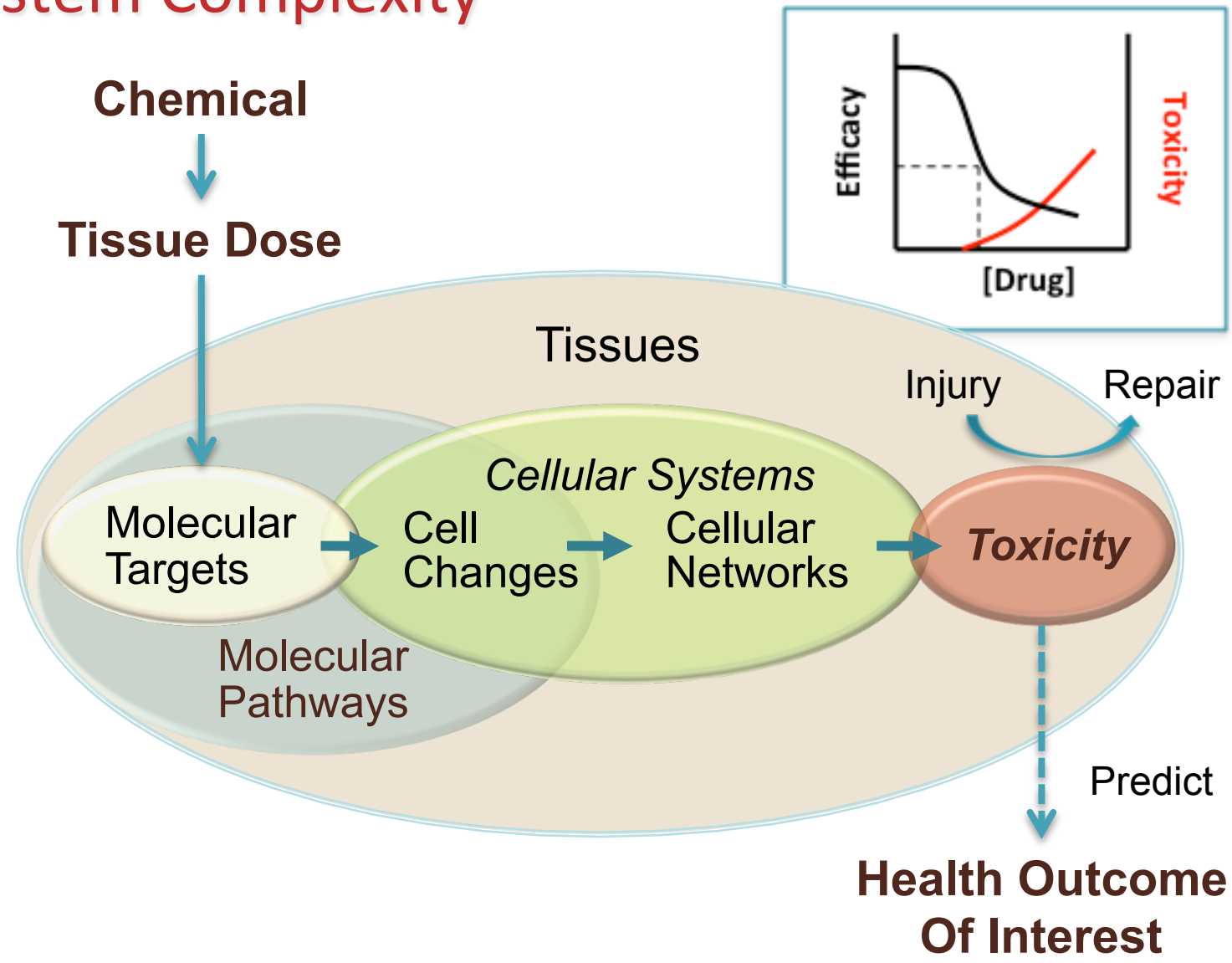
"Models are to be used, not believed."

- Henri Theil (econometrician)

"All models are wrong, but some are useful"

- George Box (statistician)

Challenges in Predicting Human Response
System Complexity



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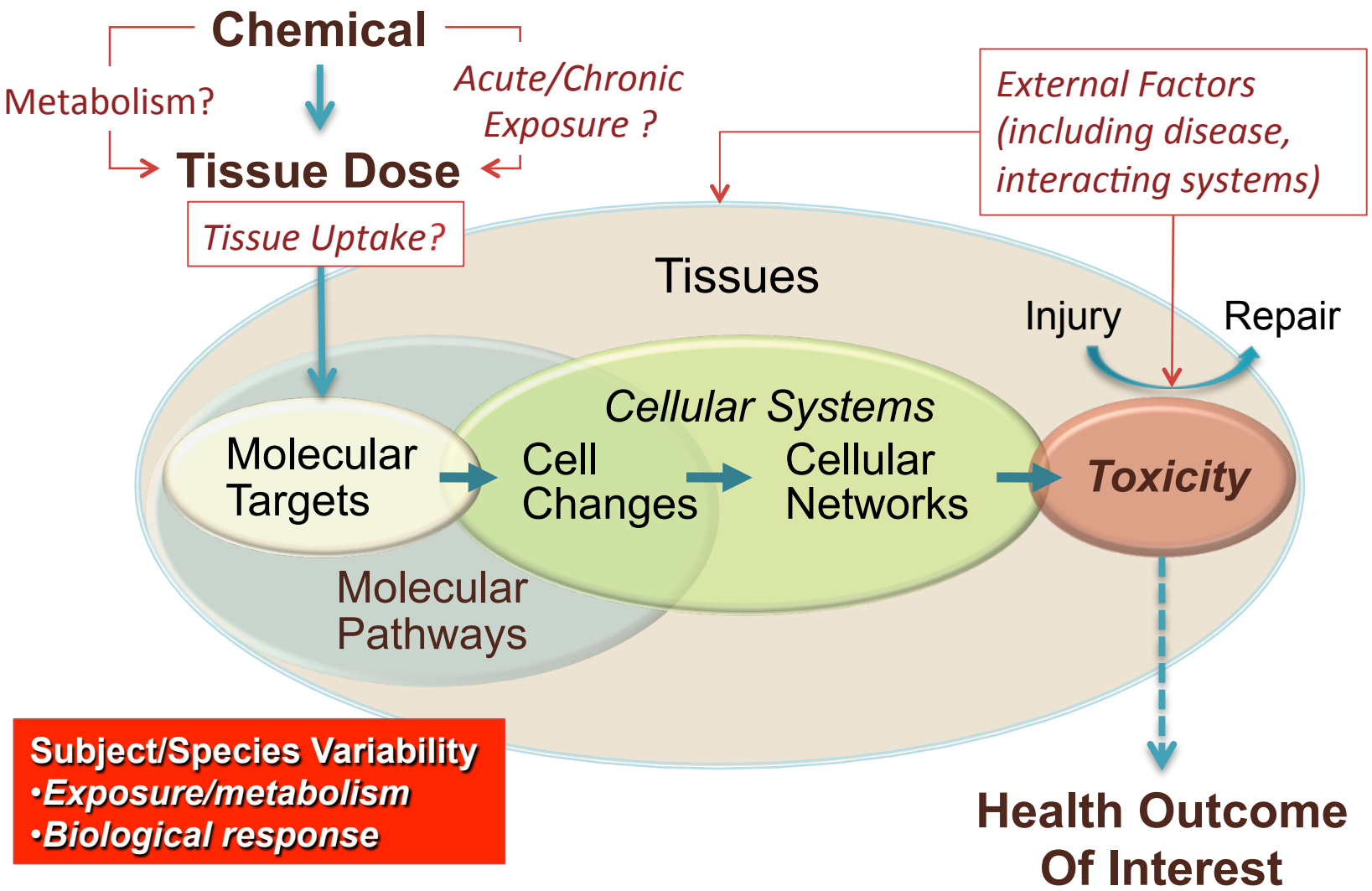
Challenges in Predicting Human Response: Outcome Modifiers



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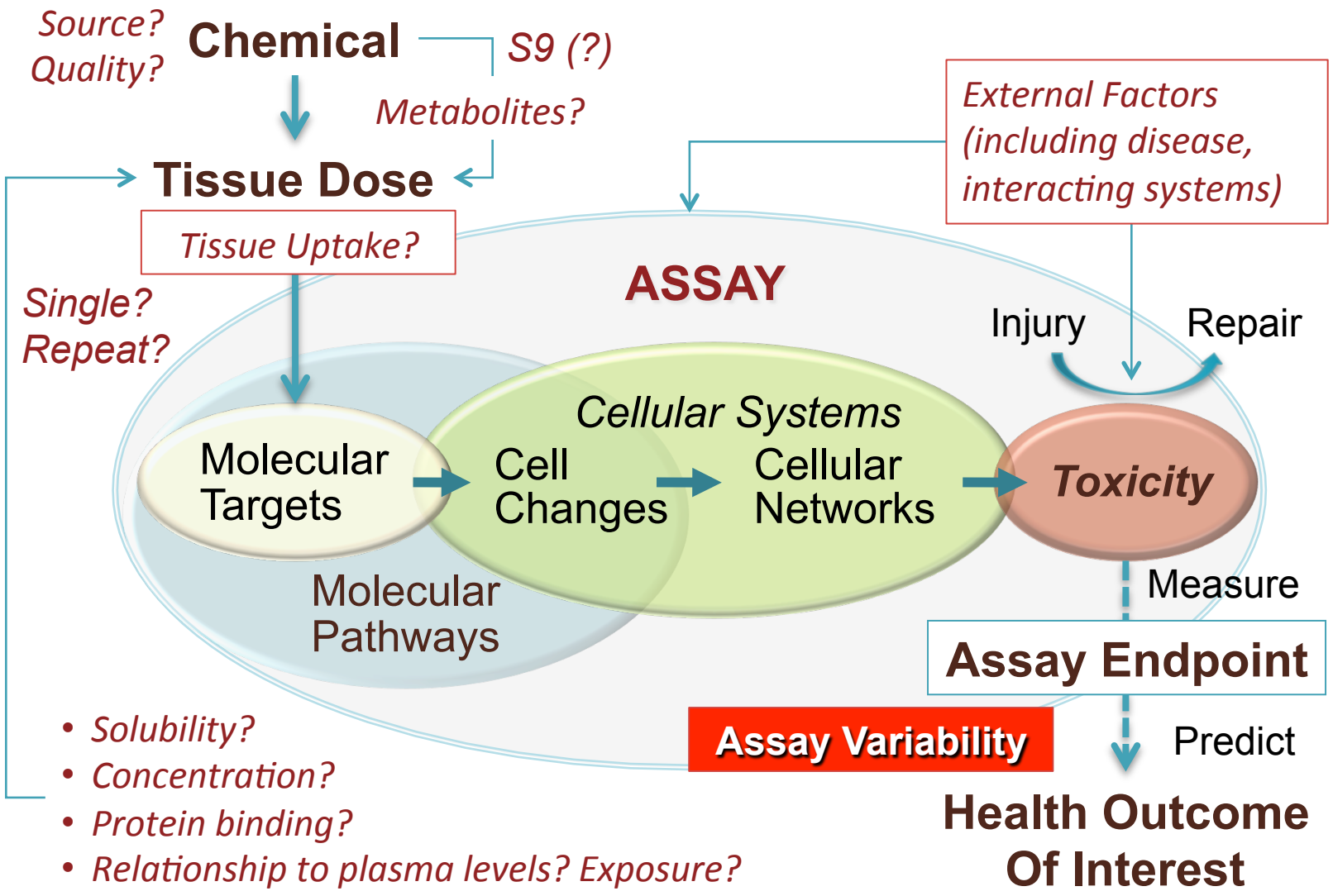
Challenges in Predicting Human Response: Assay Considerations



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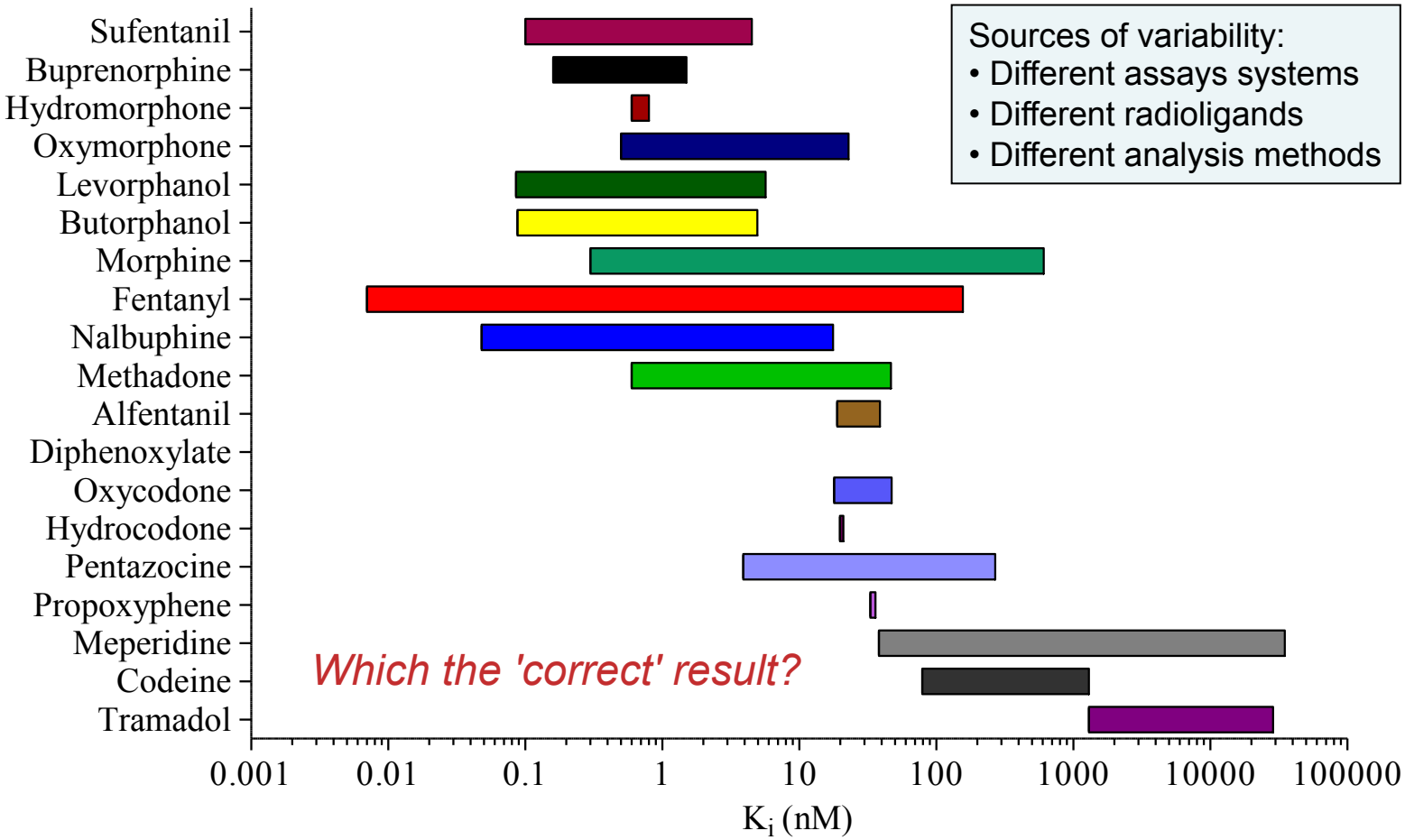
Critical Issues in Using In Vitro Models

- Cells don't get disease
- Not all compounds can be screened in vitro
- Many compounds undergo metabolism
- Results depend on study conditions, may vary widely
- Need to extrapolate from cell to organ, acute to chronic
- Need to be extrapolate from in vitro concentrations to plasma/tissue levels and in vivo doses
- Need to understand toxicity mechanisms and confirm the presence of human toxicity/disease pathways
- Need to consider the relation to human toxicity
- How to predict human variability?

Assay Data Can Show Significant Variability



Sources of variability:
- Different assays systems
- Different radioligands
- Different analysis methods

As much as 10- to 100,000-fold K_i differences observed, e.g. literature K_i values for the reference drug morphine ranged from 0.3-611 nM

Volpe et al. (2011) Regul Toxicol Pharmacol 59:385-90

From Assay Endpoints to Toxicity and AEs

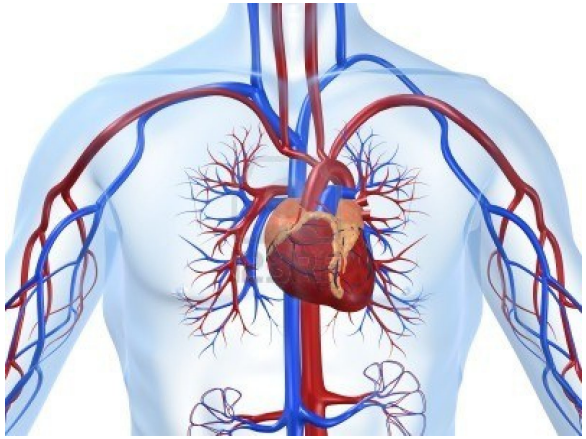
Example:
How is cardiotoxicity defined → What can be measured in vitro?

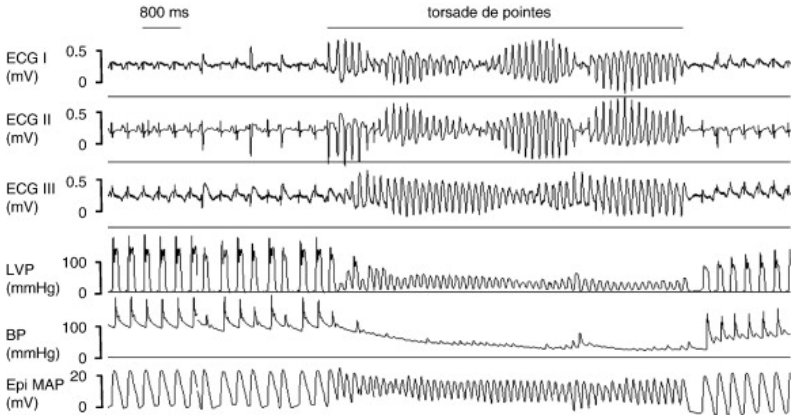
Toxicity mechanisms

- Cellular/biochemical changes
- Structural changes
- Functional changes
  - Electrical
  - Mechanical
  - Pressure/flow

Clinical manifestations

- CHF / myopathy
- Valvulopathy
- Arteriopathy
- Arrhythmias (QT/non-QT)
- High/low blood pressure





From Coker (2008) Pharmacology & Therapeutics

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DRUG DEVELOPMENT TOOLS: QUALIFICATION AND CONTEXT OF USE

FDA and Alternative Testing

"… There are still many areas where animal testing is necessary and non-animal testing is not yet a scientifically valid and available option. However, FDA has supported efforts to reduce animal testing. In addition, FDA has research and development efforts underway to reduce the need for animal testing and to work toward replacement of animal testing."

http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194932.htm

Drug Development Tool Qualification

- FDA program that provides a mechanism for formal review by CDER to qualify new tools that would broadly benefit drug development
- Currently, 3 programs have been implemented:
  - Biomarkers
  - Clinical outcome assessments
  - Animal models
- **Qualification does <u>not</u> apply to:**
  - **Assays**
  - **Computational models**
- Are qualification <u>concepts</u> useful in developing tools for general use in drug R&D and regulatory decision making?

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

Assay Validation and Qualification

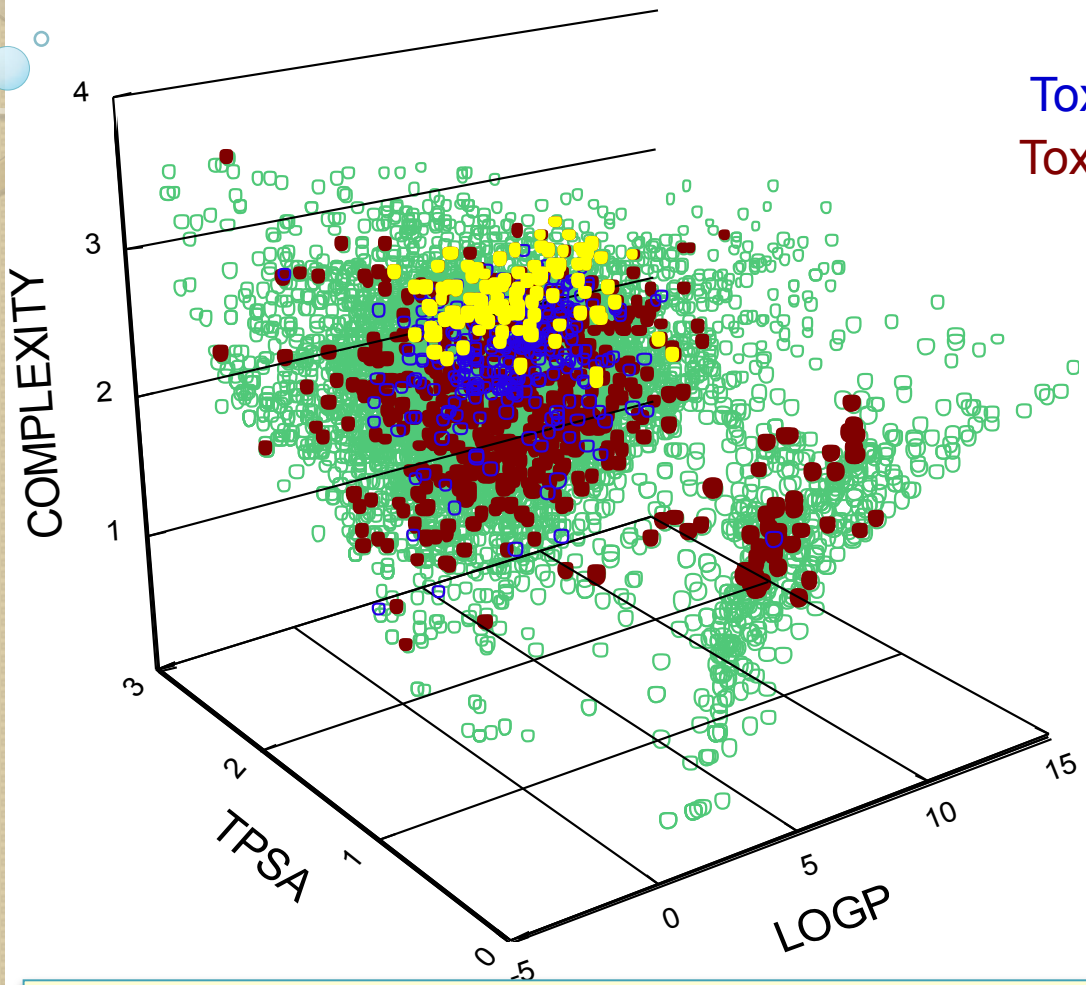
- Technical Assay Data
  - Measurement methodology (performance characteristics)
  - Physical devices used
  - Specialized software needed
  - Key operating characteristics of the measurement system
  - General availability of the components (as compared to components possessed only by the submitter and not available to organizations outside the submitter group)

- Context of Use
  - Concept to be measured
  - Targeted claims
  - Role of the planned measure in drug development
  - Justification for the proposed context of use

Development and External Validation of In Vitro Models: Use of Test Compounds

- Exemplar compounds are commonly used as standards to validate new assays and models:
  - Testing for physiological competence
  - Positive/negative controls for drug efficacy
  - Positive/negative controls for drug toxicity
- Many exemplar compounds are non-specific and exhibit other types of activity
- Many toxicities involve interactions between multiple systems and their response
- Not all compounds are assay-friendly!
  - Drugs occupy a small part of total chemistry space

ToxCast/Tox21 Libraries: Chemical Space



ToxCast_Phase I

ToxCast_Phase II

Drugs

Tox21

"ADME" Space (Lipinski)

- LOG P = -0.4 - +5.6
- Molar refractivity: 40 – 130
- MW: 160 – 500
- # atoms: 20 - 70
- TPSA $\leq$ 140 A

- LOG P = log (Octanol/Water Partition Coefficient)
- TPSA = Total Polar Surface Area
- Complexity = log (complexity based on paths, branching, atoms)

Chemical properties computed using "Adrianna" software by Molecular Networks.

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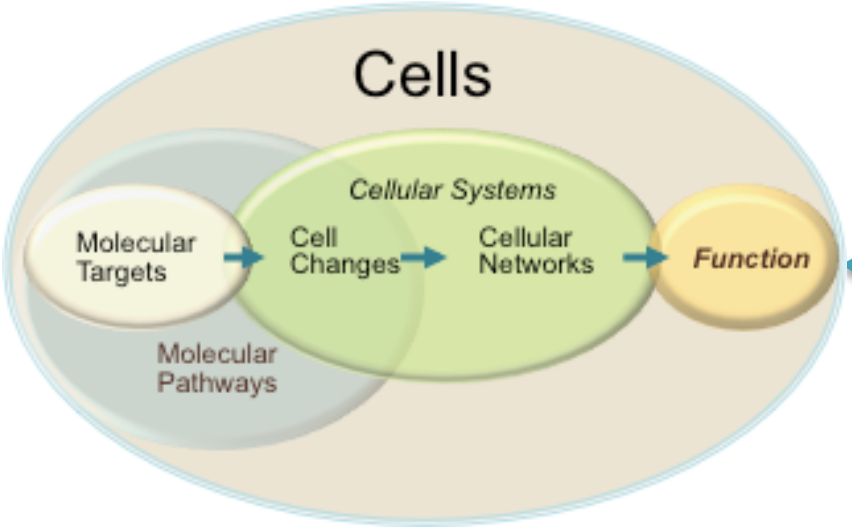
Criteria for Selecting Test Compounds

Need to demonstrate:

- Do in vitro models respond to test compounds with the expected organ-specific effects?
- Do more complex in vitro (organ) models respond to test compounds with the expected systemic effects (function / toxicity)?
- Selection of test compounds should consider:
  - Individual cell function → target organ toxicity
  - Individual organ function → linked organ function
  - Direct organ toxicities → dependent organ toxicities
  - Assay read-outs? → health outcomes of interest?

A Possible Chemical Testing Paradigm for Complex In Vitro Assays



Test Compounds # 1

Evaluate and optimize cell response

3D organ structure assemblies

Test Compounds # 2

Evaluate and optimize organ response

Linked multiple organ systems

Test Compounds # 3

Evaluate and optimize system response

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Defining Endpoints

- Many different kinds of organ toxicity
- Various ways to assess organ toxicity
  - Altered changes in function
  - Biomarkers (gene, protein, biochemical, IHC)
  - Histological changes
- Many in vitro assays rely on similar endpoints to assess pharmacological/toxicological effects
- Are there specific (human) outcome data that can be used to benchmark assay predictions?
- Linking concentrations to exposures and doses?

Drugs Adversely Affecting Function

Examples:

- Drugs that cause QT prolongation
- Drugs that increase blood pressure
- Drugs that cause immunosuppression (e.g., challenge the system with a relatively benign infectious agent, etc.)
- Drugs that cause severe headaches, dizziness, mental alertness, nausea, severe skin rash, insomnia, and other patient reported outcomes
  - May need new measures/biomarkers of function

Drugs Producing Toxicity

Examples:

- Organ-specific toxicities:
  - Liver: hepatocyte injury, functional deficits (including metabolic changes, failure)
  - Heart: contractile failure, remodeling, lesions
  - Kidney: diuresis, tubular necrosis, failure
  - Pulmonary: obstruction, necrosis, edema
- System-dependent organ toxicities
  - Adverse systemic effects downstream from tissue with the drug target
  - Drugs for which metabolism is important
  - Drugs that induce a cytokine storm

Some Examples: Possible Test Compounds

(1) To assess functional competence of the tissue/system	
Endogenous regulators	Neurotransmitters (e.g. acetylcholine, norepinephrine); cytokines (e.g. TNFα, IFN γ, IL-6), hormones, others
Functional probes	e.g. CYP, transporter substrates
(2) To assess pharmacological competence (efficacy, toxicity) at organ/system levels	
Cancer	e.g. Anthracyclines, tyrosine kinase inhibitors, 5-Fluorouracil, platinum-based drugs
Cardiovascular	e.g. Calcium channel blockers; α / β receptor blockers, Na channel blockers; QT prolonging drugs; drugs producing cardiac failure; drugs increasing heart attack risk
Liver	e.g. Direct liver toxicants; drugs with reactive metabolite; drugs associated with idiosyncratic liver toxicity
Renal	e.g. Interstitial nephritis; tubular toxicity; microvascular toxicity
Pulmonary	e.g. Bronchodilators/constrictors; inflammation/fibrosis
Neural	e.g. Developmental; direct neurotoxicants

Context of Use

- Key concept in the qualification process
- Refers to a clearly articulated description delineating the manner and purpose of use for the tool (when and how will it be used?)
- Also defines the boundaries for which the available data justify the use of the tool
- Models and assays are inevitably associated with limitations, so it is important to define:
  - The context in which results are intended to be used
  - The specific human outcomes that will be predicted

Preclinical Data in Drug Development and Possible Contexts of Use

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Preclinical pharmacology

- Suggest a reasonable mechanism of action
- Assess an appropriate dosing schedule
- Justify drug combinations
- Understand effects at the molecular target
- Identify and evaluate biomarker performance

Preclinical toxicology

- Select a safe starting dose in humans
- Gain an understanding of target organ toxicity and its potential reversibility
- Estimate the margin of safety between a clinical and a toxic dose
- Predict pharmacokinetic and pharmacodynamic parameters

Summary

- FDA is supporting efforts to reduce animal testing
- CDER's qualification process does not apply to assays, but its concepts may be useful when evaluating appropriateness of assays for broad use in drug development:
  - Technical specifications
  - Context of use
- Can the application of new in vitro technologies to drug discovery improve candidate selection and reduce attrition due to efficacy?

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Thank you!

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