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What is the Role of GLPs in ADME?

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Agenda

- Historical place of GLP in drug development
- What are GLPs? What's involved?
- Relevance to ADME?
- GLP ADME in the real world
- “Spirit of GLP”
- Why do we care?
- Future role of GLPs in ADME?

GLP History

- Why? What prompted GLP development?
- Start with the Federal Food, Drug and Cosmetic Act (FFDCA).
 - **Responsibility** for establishing safety and efficacy of human and veterinary drugs and devices and safety of food and color additives is placed on the **Sponsor** of the product
 - FDA is responsible for reviewing test results submitted to establish safety and efficacy
 - FDA regulations and guidelines prescribe what types of tests are required

Excellent source: "Good Laboratory Practice Regulations, 4th ed." Edited by S. Weinberg. Informa Healthcare USA, 2007

GLP History

- Back in the mid-1970's...
 - Ongoing assumption – reports submitted accurately described study conduct and precisely reported the data
 - Suspicion raised based on FDA review
 - Studies submitted by a major Pharma company
 - Supporting 2 important products
 - Inconsistencies and evidence of unacceptable lab practices

GLP History

- FDA inspected the lab – “For cause”
 - Not a routine practice then (primarily focused on manufacturing inspections)
 - Findings reported by FDA commissioner in a statement in a Senate hearing (1975)
 - Defects in design, conduct, and reporting of animal studies
 - Additional for-cause inspections conducted at several laboratories
 - Similar problems!

GLP History

- Deficiencies (*listed in the preamble to GLP regulations*)
 1. Experiments poorly conceived, carelessly executed, or inaccurately analyzed or reported
 2. Technical personnel unaware of importance of protocol adherence, accurate observations, drug administration, record keeping
 3. Lack of supervision and critical review of data by management
 4. Protocol designs did not allow evaluation of all data
 5. No insurance of qualifications and training of personnel
 6. Disregard for proper lab, animal care, data management procedures
 7. Inadequate monitoring of CROs by Sponsors
 8. Accuracy and completeness of data in reports not reviewed adequately before submission

GLP History

- Problems in two labs were severe
 - Previously responsible for 1000's of studies supporting drugs, pesticides, food additives
 - Extended to Environmental Protection Agency (EPA) studies as well (independent audit → 85% of EPA studies were invalid!)
 - Labs were shut down
 - 3 of 4 officials of one lab convicted of criminal charges of fraud

GLP History

- FDA response to the problem
 - Bioresearch Monitoring Program established 1976
 - 4 Task Forces handled different components
 - US Congress provided \$16 M and personnel
 - Toxicology Monitoring Task Force evaluated 7 approaches
 - Chose publication of *GLP regulations* as the best to ensure study validity

GLP Timeline

Year	Issued
1978	Final FFDCA GLP Regulations Issued (Effective 20 June 1979)
1981	OECD GLP Principles adopted
1983	Final EPA GLP Regulations
1987	Revised FFDCA GLP Regulations*
1989	Revised EPA GLP Regulations
1997	Revised OECD GLP Regulations

*Further revisions reflected in current FFDCA GLP guidelines up to March 4, 2002

GLP in Practice

- Testing facility shall submit to FDA inspection
- Personnel
 - Appropriate education, training, and experience
 - Training records
 - Sufficient staffing
 - Safety precautions, lab clothing, etc.
- Testing facility management
 - Designated study director – defined responsibilities
 - Quality Assurance Unit (QAU)
 - Management responsible for facility, personnel, resources, maintenance of test articles, etc.

GLP in Practice

- Study director – overall responsibility for technical conduct, interpretation, analysis, documentation, reporting, etc.
- QAU
 - Maintains master schedule, protocols, etc.
 - Periodic inspections of each GLP lab study
 - Review final study report for accuracy, integrity
- Facilities
 - Suitable size and construction
 - Animal care
 - Animal supply
 - Handling test and control articles
 - Lab operation areas
 - Specimen and data storage areas

GLP in Practice

- Equipment
 - Appropriate design
 - Maintained and calibrated
 - Standard Operating Procedures (SOPs) for this
 - Records maintained of inspection, maintenance, calibration, standardization, etc.
- Testing facilities operation
 - SOPs
 - Nonclinical laboratory study methods
 - List of minimum specific areas requiring SOPs

GLP in Practice

- Testing facilities operation (cont)
 - Reagents and solutions
 - Animal care
 - Housing, feeding handling, etc.
 - Separate housing different species
 - Cleaning, sanitation of facility
 - Feed and water analyzed
 - Pest control

GLP in Practice

- Test and control article
 - Characterization – identity, strength, purity, etc.
 - Stability
 - Labeling
 - Formulated article storage, testing, strength, etc.
- Protocol
 - Signatures
 - Covers all aspects of a nonclinical lab study

GLP in Practice

- Records and reports
 - Report covers all facets of the study (listed in regs)
 - Storage and retrieval of records and data
 - Retention of records
- Disqualification of testing facilities (lengthy discussion)

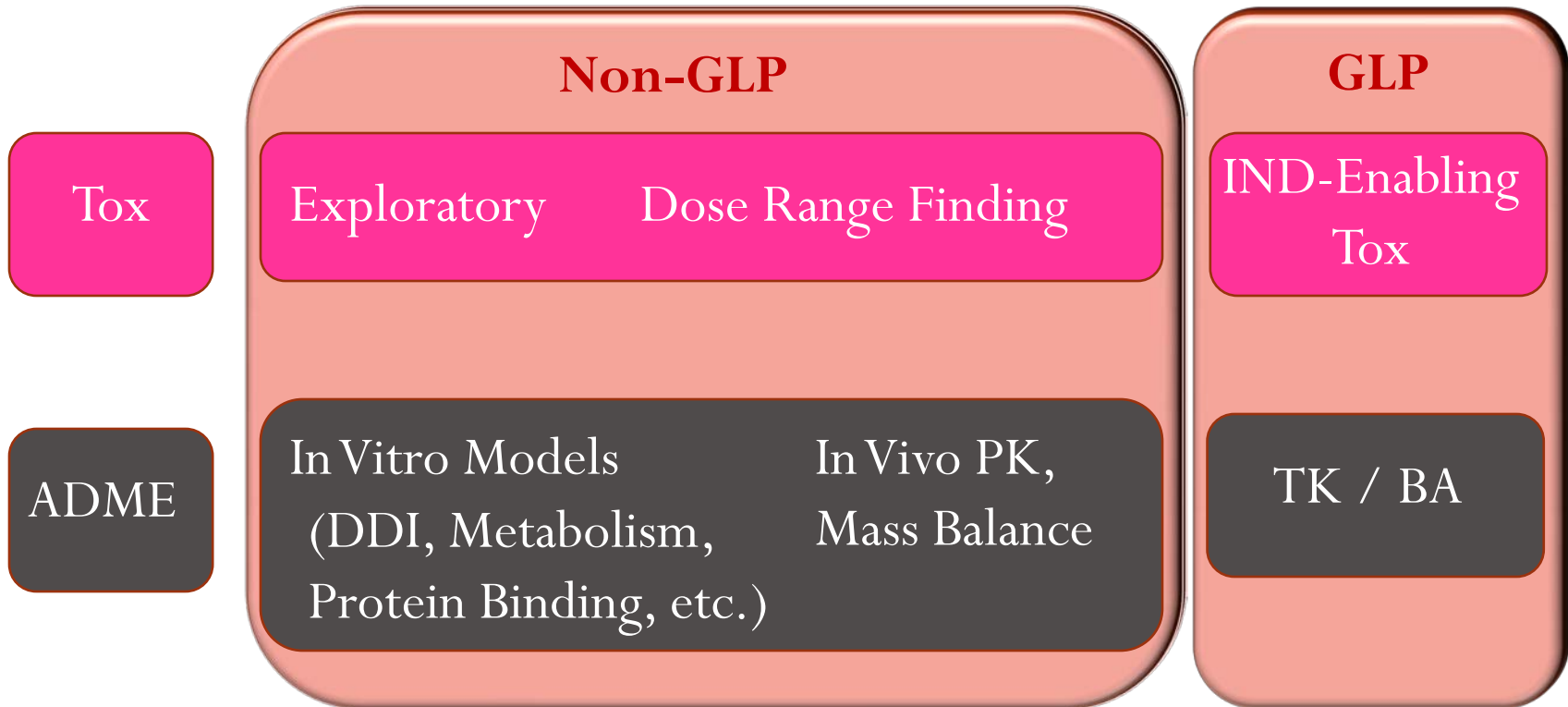
GLP Relevance for ADME?

- Presently well accepted role in:
 - Bioanalysis for toxicokinetics (TK)
 - For support of GLP toxicology studies
 - Validation
 - Study sample analysis
 - ICH S3A
- Tacitly accepted role in:
 - TK analysis and reporting
 - *In vitro* membrane permeability (e.g. Caco-2) in support of Biopharmaceutical Classification System (BCS) biowaiver

GLPs in Development

Development Timeline

Candidate  IND



GLP Scope (ADME?)

- 21 CFR Part 58, Subpart A §58.1 – Scope
 - This part describes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications... Compliance to this part is intended to **assure the quality and integrity of the *safety* data** filed...
- 21 CFR Part 58, Subpart A §58.3 – Definitions
 - Nonclinical laboratory study means *in vivo* or *in vitro* experiments in which test articles are studied prospectively in test systems under laboratory conditions **to determine their safety**.
 - ... does not include basic exploratory studies carried out to determine whether a test article has any potential utility...

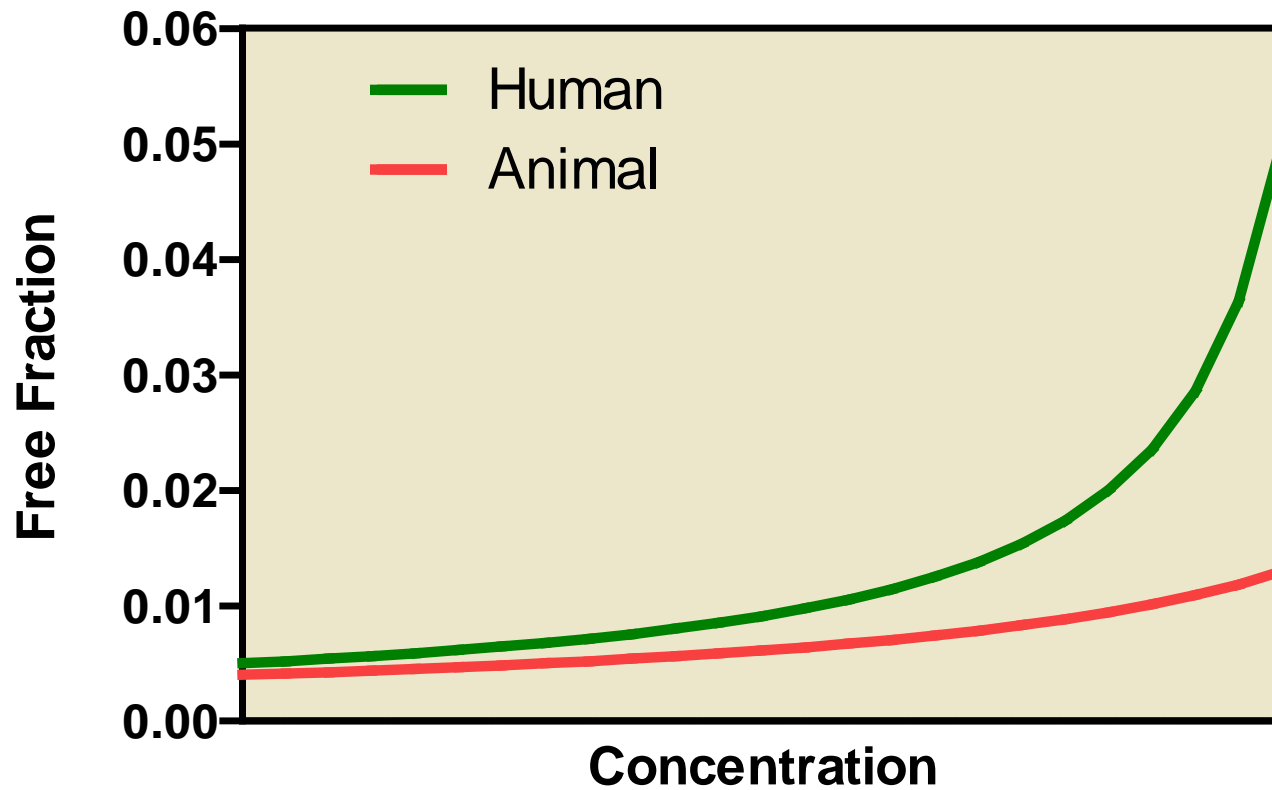
GLP Scope (ADME?)

- One interpretation¹
 - The following are examples of studies to which the GLPs *can* apply: ...*(xxi)* target animal absorption, distribution, metabolism, and excretion (ADME)...
- Recent personal experiences
 - Former FDA Pharm/Tox Reviewers

¹*Peterson WA. FDA/GLP Regulations. In "Good Laboratory Practice Regulations, 4th ed."*
Edited by S.Weinberg. Informa Healthcare USA, 2007. pp 25-110

Interpretation!

- What defines “safety?”



In the Real World

Regulatory Hurdles

- Scientific advances
 - Increased methodological rigor and scope
 - Bioanalytical – ISR's
 - Wider application of GLPs
 - Increased awareness of additional factors that have a large impact in optimizing therapy
 - Transporters
 - Drug-Drug Interactions (new FDA guidance)

R. Guttendorf. ADME and Predictive Tox. Meeting. 14 March 2012

In the Real World

Meeting the demands of regulatory requirements: the significance of ADME

Bioanalysis (2012) 4(12), 1395–1397

their development candidates. In my consulting practice I have seen a surprising increase in the number of small pharma clients needlessly insisting that non-clinical ADME studies be performed according to Good Laboratory Practice (GLP) guidelines. The perception is that GLP means 'better'. Insofar as GLPs dictate strict documentation and quality assurance oversight, there is a kernel of truth in this belief. In reality, however, GLP adherence provides only a marginal enhancement in quality above a study conducted 'in the spirit of GLP', that is, 'GLP without the extra paperwork'.

Current Positions and Practice

- “Most pre-clinical studies must adhere to GLP to be acceptable for submission to regulatory agencies such as FDA in the US” (*Wikipedia... so, take with a grain of salt*)
 - Preclinical studies = ... PD, PK, ADME, and toxicity testing
- “GLP for ADME is not required in all cases but recommendable (if you base any safety evaluations on your ADME data)” (*PharmPK discussion board, 2006*)

Current Positions and Practice

- “Many researchers are under the mistaken impression that at the IND stage all studies must have GLP documentation... FDA requires GLP... for **only safety studies**. GLP is **NOT** required for... *in vitro* studies, including PK analyses that support *in vivo* efficacy and toxicity studies; DDI studies, *in vitro* ADME studies.” (www.apredica.com/glp.php)

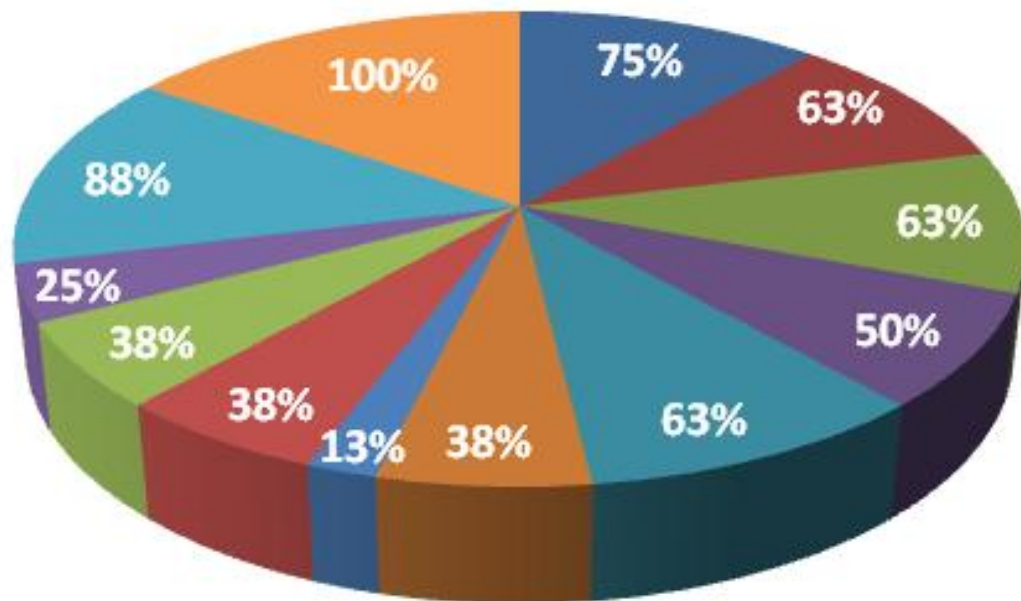
In the Real World – CRO Perspectives

- Survey conducted
 - 9 large, established CROs solicited; 8 replied
- Some questions
 - Do you offer GLP-compliant ADME studies?
 - If so, which types of studies are offered with GLP oversight (survey included 12 specific examples)?
 - What percent of ADME work solicited is requested to be GLP?
 - Trends in past 5-10 years?
 - Will GLP ADME become the norm in the future?

CRO Survey

Do you offer these assays with GLP compliance?

% "Yes" Responses

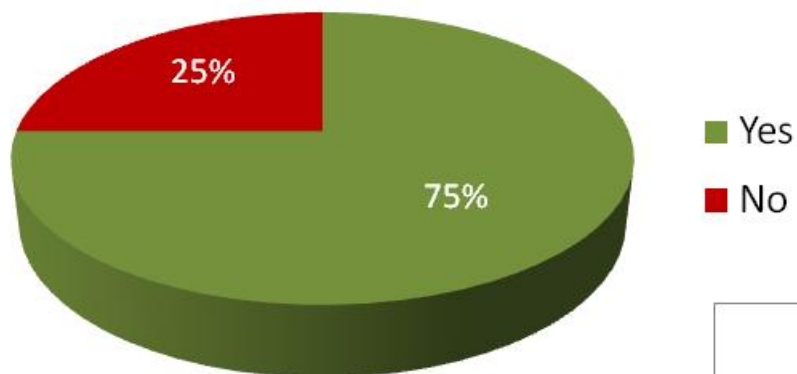


- Protein Binding
- RBC Distribution
- CYP Inhibition (microsomes)
- CYP Inhibition (hepatocytes)
- In Vitro CYP Induction
- In Vitro Metabolic Stability
- In Vitro Metabolite Profiling
- Reaction Phenotyping
- Transporter Assessments
- In Vitro Membrane Permeability
- In Vivo Animal PK
- In Vivo Animal ADME (radiolabel)

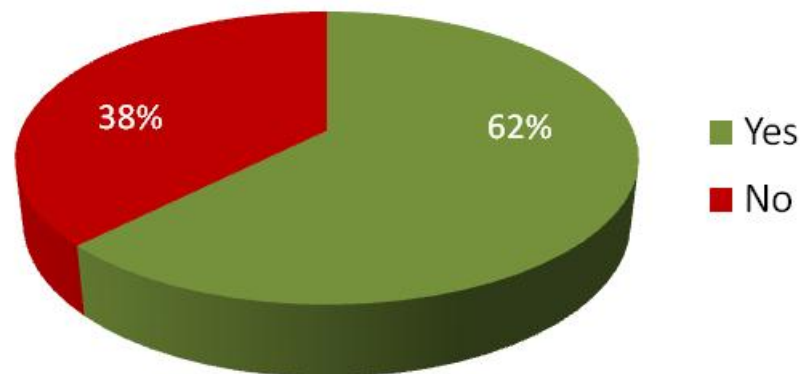
CRO Survey

Do you offer these assays with GLP compliance?

Protein Binding



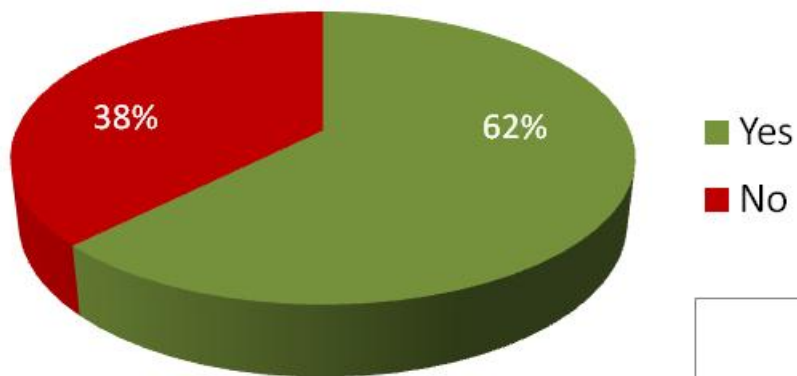
RBC Distribution



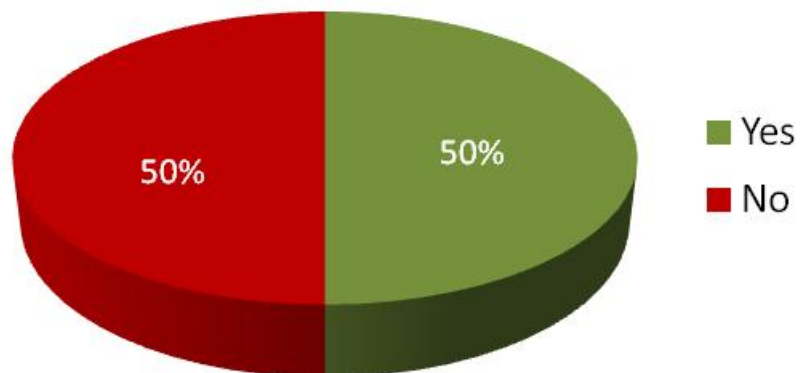
CRO Survey

Do you offer these assays with GLP compliance?

CYP Inhibition (Microsomes)

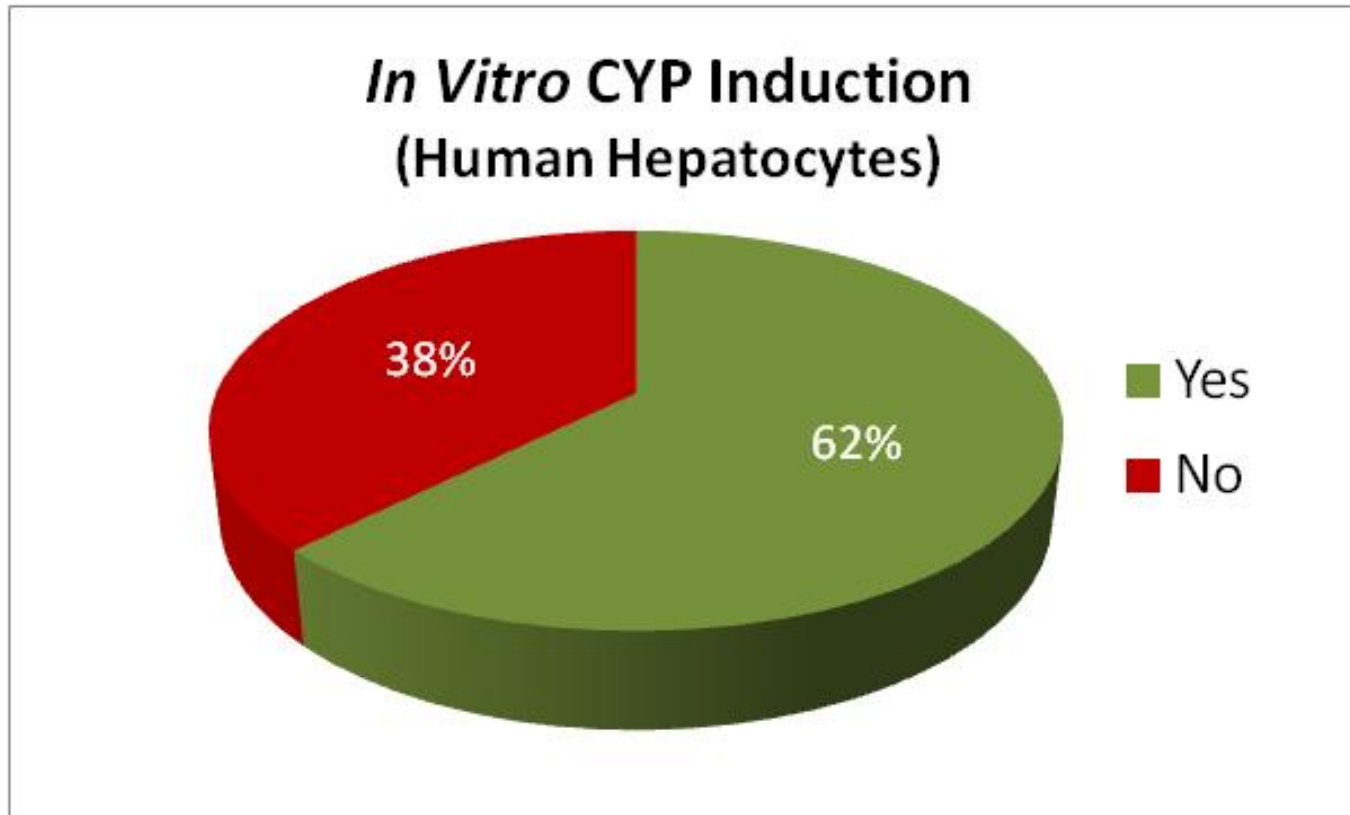


CYP Inhibition (Hepatocytes)



CRO Survey

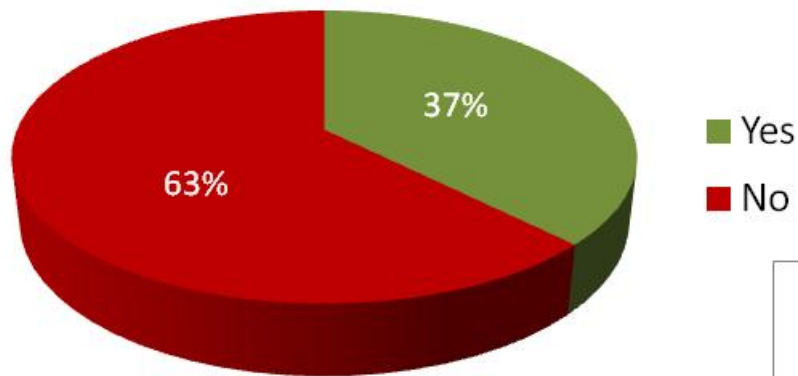
Do you offer these assays with GLP compliance?



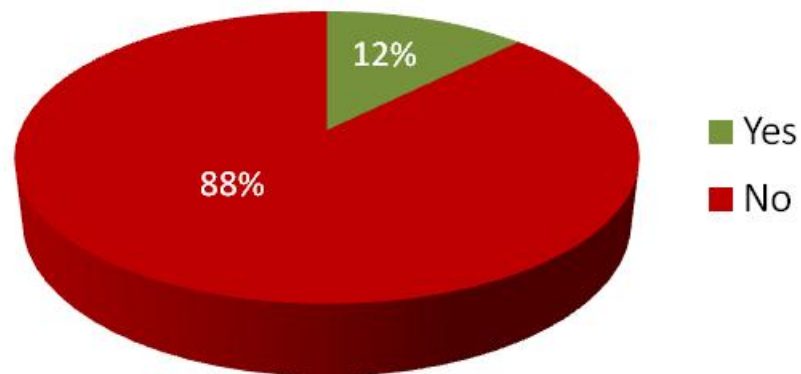
CRO Survey

Do you offer these assays with GLP compliance?

***In Vitro* Metabolic Stability**

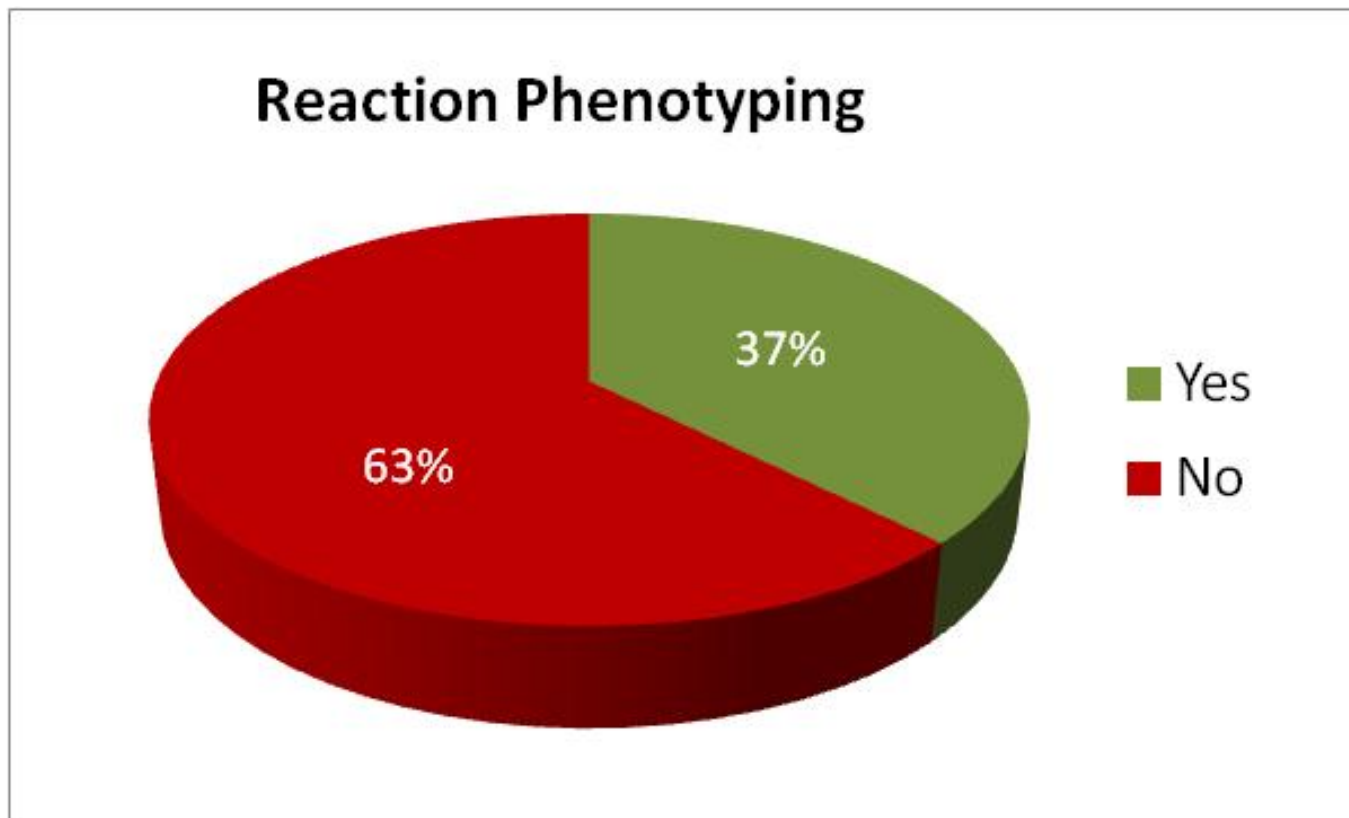


***In Vitro* Metabolite Profiling**



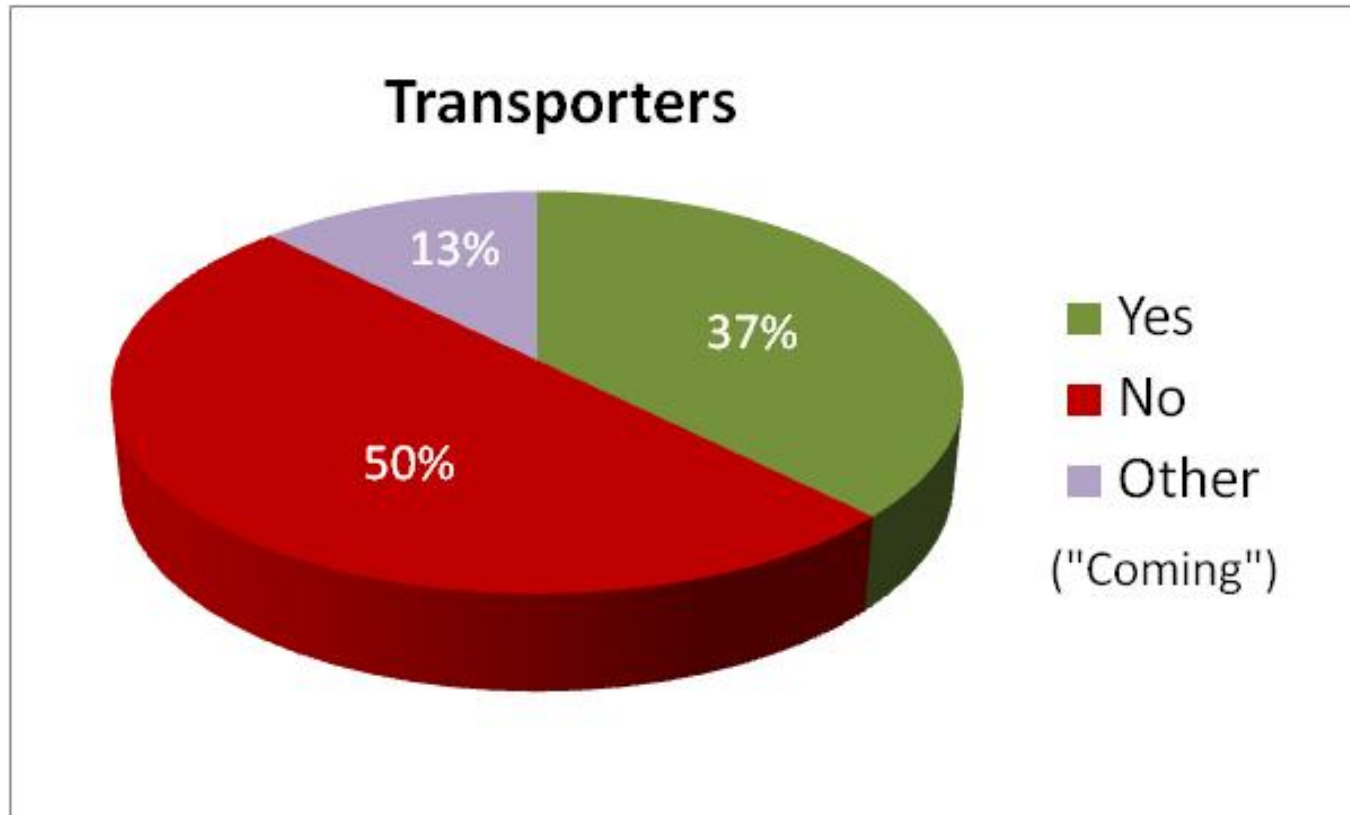
CRO Survey

Do you offer these assays with GLP compliance?



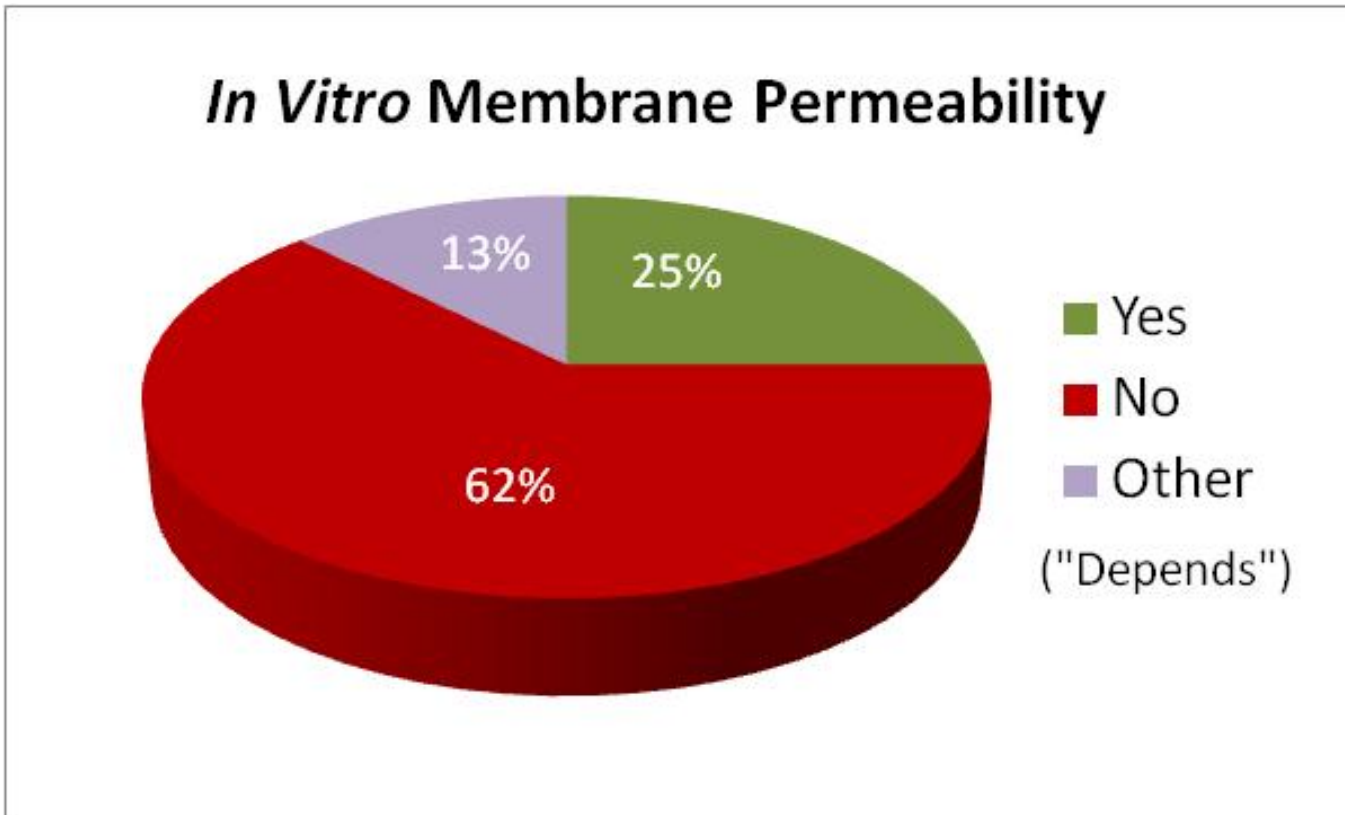
CRO Survey

Do you offer these assays with GLP compliance?



CRO Survey

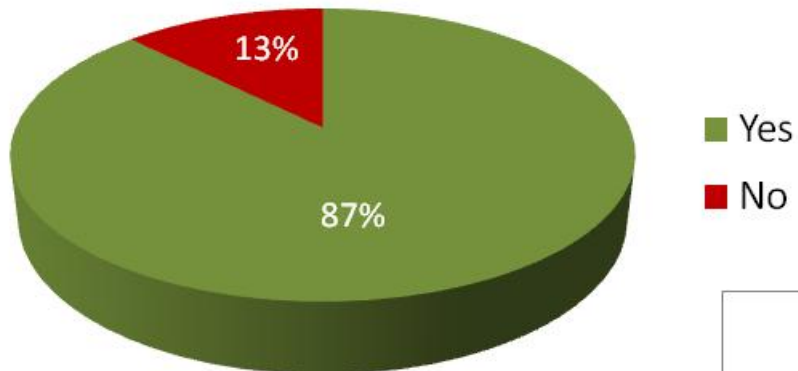
Do you offer these assays with GLP compliance?



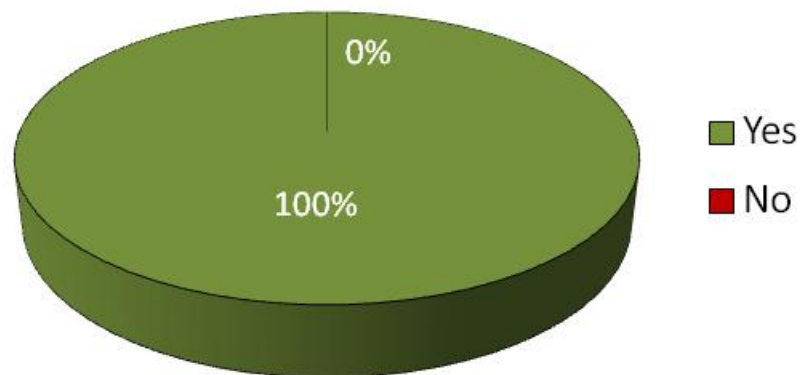
CRO Survey

Do you offer these assays with GLP compliance?

In Vivo Animal PK



In Vivo Animal ADME (Radiolabel)



CRO Survey

Do you offer these assays with GLP compliance?

- Others?
 - *In vitro* permeability to support BCS (Biopharmaceutical Classification System) biowaiver (N=1)
 - 100% of requests for this are for GLP

CRO Survey

% of Service Requests for GLP

- 5%: N=2
- 5-10%: N=2
- 10%: N=1
- 20%: N=1
- 50%: N=1
- 100%: N=1 (BCS only)
- Not specified: N=1 “...only get requests for GLP for mass balance and QWBA” (this group offers all but metabolite profiling as GLP)

CRO Survey

Profile of Sponsors Requesting GLP ADME

- No specific profile (N=1)
- Small Pharma or Biotech (N=2)
 - “Even after being advised that it is not needed”*
- Non-USA clients (N=2)
- Large Pharma (N=1)
 - Mass balance and QWBA

*The company that did 50% of studies by GLP

CRO Survey

Trends in Frequency of Requests for GLP ADME

- ...in the past 5-10 years?
 - Decreasing (N=2)
 - About the same (N=4)
 - Drastic increase (N=1) for BCS (others fairly constant)

CRO Survey

Other Trends?

- Seeing a decrease in requests as large Pharma staff (“who know GLP is not required”) are relocating
- More requests for QA oversight but not full GLP

CRO Survey

Will GLP ADME be the norm in the future?

- NO (N = ALL!)
 - “Based on 15 years of trends”
 - “Not required by regulatory bodies... adds expense, not quality”
 - “Mostly due to expense”
 - “Pharma industry not willing to pay for this”
 - “More work will be done NON-GLP due to economic factors”
 - “More large Pharma outsourcing will ↓ proportion of GLP”
 - “Full validation of supporting analytical methods would take much longer than the study itself (but study procedures themselves should be controlled)”

CRO Survey

Will GLP ADME be the norm in the future?

- NO (N = ALL!) ... *continued*
 - “Part 58 GLPs only apply to TOX studies”
 - “GLPs would have to be re-written to accommodate ADME”
 - “These studies are investigational in nature”
 - “We hope not! Feel it is not a good use of money”
 - Spirit of GLP seems to be a well accepted compromise

CRO Survey

Miscellaneous thoughts

- “GLP does not equate with better quality, just a lot more paperwork”
- “Most ADME studies better served with a fit-for-purpose model... more rigor should be applied to analysis as compound proceeds through development”
- “There are fewer scientist who really understand the area and the studies”
- “We counsel sponsors to run ADME as non-GLP”
 - QA review an option
 - Costs are higher and report will have multiple GLP exceptions
- “We run all our studies to GLP standards, just no QA audit” (*Spirit of GLP*)

Current Compromise: “Spirit of GLP”

- Very common practice for nonclinical ADME
 - Also applies to non-GLP safety studies
- What does it involve?
 - SOPs in place and adhered to
 - Well-controlled protocols
 - High scientific integrity – controls, standards
 - Designated study director
 - *Less documentation and no QA oversight*

Current Compromise: “Spirit of GLP”

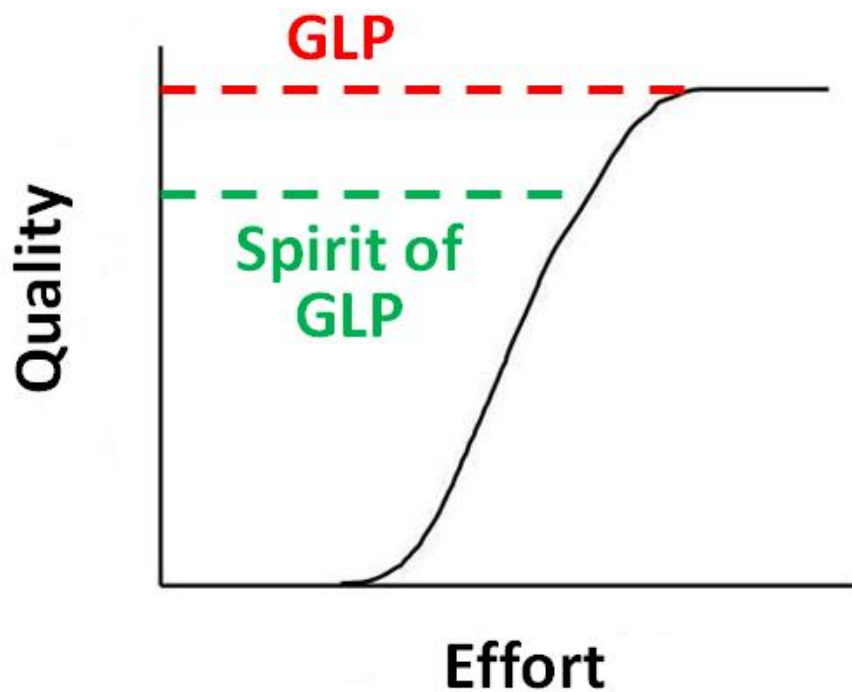
- What is missing?
 - Master study schedule (trigger for FDA audit)
 - Records and Documentation (maybe, maybe not)
 - SOPs – electronic and paper
 - Production papers
 - Inventory records – track back, track forward
 - Test article and sample handling and tracking
 - Preventive maintenance
 - Data handling, storage, retrieval
 - Maintenance and calibration of equipment
 - Personnel records
 - Audit trails
 - Regulatory reports (Audits)

Current Compromise: “Spirit of GLP”

- What is missing? (*cont.*)
 - Full (bio)analytical method validation
 - Dose solution analysis with validated method
 - Certificates of analysis for all analytes (characterization, stability, storage)
 - Facility and study QA audit/review
 - No record of GLP exceptions

GLP vs. “Spirit of GLP”

Documentation Quality



Scientific Quality



Lessons from History and Trends

- “ADME will be GLP... just a matter of time”
 - Consider Safety Pharmacology
- TK – BA vs. TK analysis and report writing
 - GLP TK analysis/reporting increasing in practice
 - Is it written?
 - Is it expected?

The Future?

- Position of former FDA Pharm/Tox reviewers is telling
 - Toxicologists vs. ADME experts
- Why would we care? ... (and we do)
 - Increase complexity of drug development
 - Lengthen development time
 - Increase development expense
- Variable impact
 - Big Pharma
 - Small Pharma/Biotech
 - (Academic labs)
 - CRO's
- Is FDA itself giving this any thought?