The VGDS Process at the US FDA: Lessons Learned and Future Directions

American College of Toxicology

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Disclaimer

- The views expressed in this presentation are the ones of the author and may not necessarily reflect the position of the U.S. Food and Drug Administration.

Outline

- **General Overview of the VGDS Program at the FDA**
- Non-clinical VGDS: Common Themes and Questions
- Biomarker Classifications in the Pharmacogenomic Guidance and the Biomarker Qualification Pilot Process
  - Overview and how it relates to Toxicogenomic VGDS sent to the agency to date
- Future Directions: VXDS

Update: VGDS Program So Far

- VGDS statistics:
  - 30 submissions received to date
  - 20 sponsor meetings held (2 bilateral with EMEA)
  - ~ 2-3 submissions per quarter

VGDS Submission Types

- **Therapeutic Areas:**
  - Cancer (multiple types)
  - Alzheimer's Disease
  - Hypertension
  - Diabetes
  - Depression
  - Obesity
  - Rheumatoid Arthritis

- **Scientific and PGx Areas:**
  - Biomarkers
  - Genotyping Devices
  - Microarrays
  - Analysis Software
  - Databases
  - Metabolic Pathways
  - Biostatistics
  - Enrichment design
  - Registry design
  - Toxicology

Data based on 30 submissions

VGDS: Value and Benefits

- Sponsor:
  - Opportunity to have informal, scientific meeting with FDA PG experts
  - Eliminate uncertainty about PG data submissions and review at FDA
  - Strategic use of VGDS
  - Receive and benefit from informal peer-review feedback on PG issues and/or questions
  - Gain insight into current FDA thinking about PG
  - May avoid future delays in review
- FDA:
  - Familiarize with PG experiments, data analysis and interpretation approaches
  - Education
  - Ensure data driven development of new policies and guidances
  - Build consensus around PG standards
- Both:
  - New strategies for using PG in drug development
  - Learn about benefits and limitations
  - Discuss analysis approaches

VGDS: Limitations

- Not a regulatory decision tool
- Not a standard submission: individual considerations
- Amount of data submitted
- Involvement of Clinical Review Division (priority)
- It’s voluntary: we may not see all there is to see

VGDS Lessons Learned

- Meeting Preparation:
  - Early communication
  - Evaluation of sponsor questions
- Data Submission:
  - Need for standards (e.g. HL7, CDISC, others)
  - Dedicated server, access rights for IPRG (intranet)
- Regulatory and Policy Impact:
  - Innovative trial designs (e.g. enrichment strategies)
  - Involvement of Clinical Review Divisions
  - Drug-Test Co-development

VGDS Lessons Learned, cont'd

- Data Review:
  - Much data/information is VERY exploratory
  - Whole genome scans (SNPs and gene expression)
  - Statistical considerations
  - Biological interpretation, e.g. pathway analysis
  - More thorough data analysis is valued by sponsors: sponsor and FDA present results
- Education:
  - Creation of FDA/CDER course on pharmacogenomics
  - Rotations in Genomics Group to expose reviewers to genomic data sets (new candidates always welcome!)
- Other:
  - Sponsors appreciate opportunity for open, informal data exchange and discussion
  - Biomarker validation critical

VGDS Impact

- Developing “Best Practices” document
  - **November 27-28, 2006:** Workshop co-sponsored by FDA, DIA, PhRMA, and Bio: Best Practices and Development of Standards for the Submission of Genomic Data to the FDA.
- MAQC (Microarray Quality Control Project)
  - provide quality control tools to the microarray community to avoid procedural failures
  - develop guidelines for microarray data analysis
  - reference datasets and reference RNA samples
- Critical need for biomarker validation
  - Developed proposed process map for validation of genomic biomarkers of preclinical drug safety
- Developing IT infrastructure to handle “-omic” data
- Statistics Task Force being created

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Non-clinical Topic Areas Covered by VGDS Submissions to Date

- Hepatotoxicity
  - PPARα
- Vasculitis
- Muscle toxicity
- Cardiotoxicity

Common Themes

- The non-clinical VGDSs received thus far can be grouped into two basic categories:

1. **The application of toxicogenomics for the development of screening tools (genomic biomarkers) for target organ specific toxicities with the goal to select the most promising candidate compound(s)**

2. The leveraging of toxicogenomic information along with classical non-clinical information in an attempt to derive more detailed insights into the molecular mechanisms of toxicity for compounds or compound series.

First Category Example

- The FDA has received a VGDS from a Sponsor that consisted of a TaqMan™ based screening system to identify specific subtypes of toxicities in the target organ of interest.
- The selection of genes to be used in the TaqMan™ based screening system were identified by mining a database of toxicogenomic information derived from microarray experiments in conjunction with classical toxicological information.
- Gene expression changes for the sub-panels of pre-selected genes were analyzed following treatment of rats with well characterized reference toxicants that induce specific types of damage to the particular target organ.
  - Each study included the classical endpoints such as clinical chemistry and histopathology results in conjunction with the gene expression data.
  - In essence, determining how the assay is performing (internal validation of the system)
- It was conveyed by the sponsor that the gene expression information was used in conjunction with preliminary ADME, pharmacological, medicinal chemistry and toxicology data to help prioritize candidate molecules during early drug development processes.

VGDS: Common Questions

Question from sponsor

- What is the appropriate classification of the genomic biomarkers that they have described in their independent submission?

FDA Answer

- Genomic biomarkers as presented in VGDS submissions to date are exploratory and lack the scientific evidence to move the markers into the "probable valid" or "known valid" category.

VGDS: Common Questions

Question from sponsor

Can the FDA comment on a novel set of genomic biomarkers such as selected gene sub-panels or signatures that are being used for a particular type of interpretation, e.g. the identification of a PPARα agonist response in a new chemical entity?

FDA Comments:

Sponsors also have requested feedback from the FDA on the biological interpretation of the gene expression information. In the broader sense, these types of submissions address the issue of how novel genomic biomarkers can be qualified for their intended use.

General Comment:

The majority of the VGDSs contain exploratory safety biomarkers that are being validated at the sponsors site for internal use in prioritizing compounds in early drug development.

Can a VGDS or VXDS be a starting point for safety biomarker validation in the near future? This will be addressed in more detail later in the presentation.

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  2. **The leveraging of toxicogenomic information along with classical non-clinical information in an attempt to derive more detailed insights into the molecular mechanisms of toxicity for compounds or compound series.**

Second Category Example

- Another VGDS focused on using a toxicogenomic approach for understanding the molecular underpinnings of toxicity for a couple of compounds in their drug development program.

- The example focused on the presence of increased quantities of peroxisomes that was not detectable via electron microscopy (the gold standard), while gene expression changes based on the microarray results provided evidence for increases in peroxisomes in rats via a PPARα agonist transcriptional response.

VGDS: Common Questions

Question from sponsor:

How does the FDA handle microarray data that had no other supportive findings, e.g. histopathology, associated with it?

FDA Answer:

In this case, clearly the absence of confirmatory results for peroxisome proliferation by electron microscopy does not allow the gene expression data to suffice on its own to support the classification for this compound; but the results could be used as part of the evidence to support the presence of increased numbers of peroxisomes.

General Observations and Important Points

- Our experience with reviewing VGDS data thus far indicates that the quality of interaction with the sponsor often directly correlates with the breadth and detail of data submitted to the agency

- VGDS meeting is a forum for scientists from the review divisions to participate
  - Ancillary data such as histopathology findings have facilitated broader participation by the FDA scientists, allow wider range of analyses, and more in-depth scientific discussions

General Observations and Important Points

- Gene expression changes versus classical endpoints
  - Gene expression changes may precede classical endpoints such as histopathology or clinical chemistry findings
- Microarray data with no associated physiological changes at the time point of interest intriguing from a scientific perspective
  - Reference database analyses, pathway analyses, and literature mining can provide scientific framework for generating hypotheses on mechanism of action
  - Improve our general understanding of early molecular events that may enable strategies for flagging critical safety issues early
  - Potentially lead to the identification of novel safety signatures (biomarkers)
- How do we move forward from exploratory biomarkers to validated safety biomarkers?

Common Themes Linked to Safety Biomarker Validation

- Sponsors also have often requested feedback from the FDA on the biological interpretation of the gene expression information that is provided in a particular VGDS project.
- In the broader sense, these types of submissions address the issue of how novel genomic biomarkers can be qualified for their intended use.
  - Potential to assess biomarker context
- The VGDS program, as well as a series of other activities initiated by the Genomics Group at the FDA (e.g. specific collaborative research efforts and a Predictive Safety Testing Consortium have led to a proposal for a formal qualification process for such biomarkers, which is currently being tested.

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Classification of Biomarkers

- **Known valid**
  - Accepted by scientific community at-large to predict clinical outcome
- **Probable valid**
  - Appears to have predictive value but not yet replicated or widely accepted
- Classification leads to specifications for validation in the context of **intended use** for biomarker

Classification of Biomarkers, cont'd

- **Exploratory Biomarkers**
  - Lay groundwork for probable or known valid biomarkers
    - Hypothesis generation
  - Fill in gaps of uncertainty about disease targets, variability in drug response, animal – human bridges and new molecule selection
    - Learn and improve success in future drug development programs
  - Can be "de novo" or "sidebar" study embedded in (pivotal) clinical efficacy trials

Known Valid

Probable Valid

Exploratory

- Examples from drugs labeled in U.S.:
  - Safety:
    - TPMT (6-MP, azathioprine)
    - UGT1A1 (irinotecan)
    - CYP2C9/VKORC1 (warfarin)
    - CYP2D6 (Strattera)
  - Efficacy:
    - EGFR status (Erbitux, Tarceva)
    - Her2/neu status (Herceptin)
    - Philadelphia chromosome ~ Bcr-abl (Gleevec)
    - C-kit (Gleevec)

Known Valid

Probable Valid

Exploratory

- Examples:
  - Safety:
    - Kim1 ~ preclinical (nephrotoxicity)
    - Gene panels used for preclinical safety evaluation
  - Efficacy:
    - EGFR mutations (Iressa)
    - CYP2D6 (Tamoxifen)
    - OncotypeDx gene panel (radiation therapy)

Known Valid
Probable Valid
Exploratory

- Examples:
  - Safety:
    - Gene panels used for preclinical safety evaluation
  - Efficacy:
    - APOE4 (Donepezil, Alzheimers)
    - VEGF (several anticancer agents)

More information available at the website below

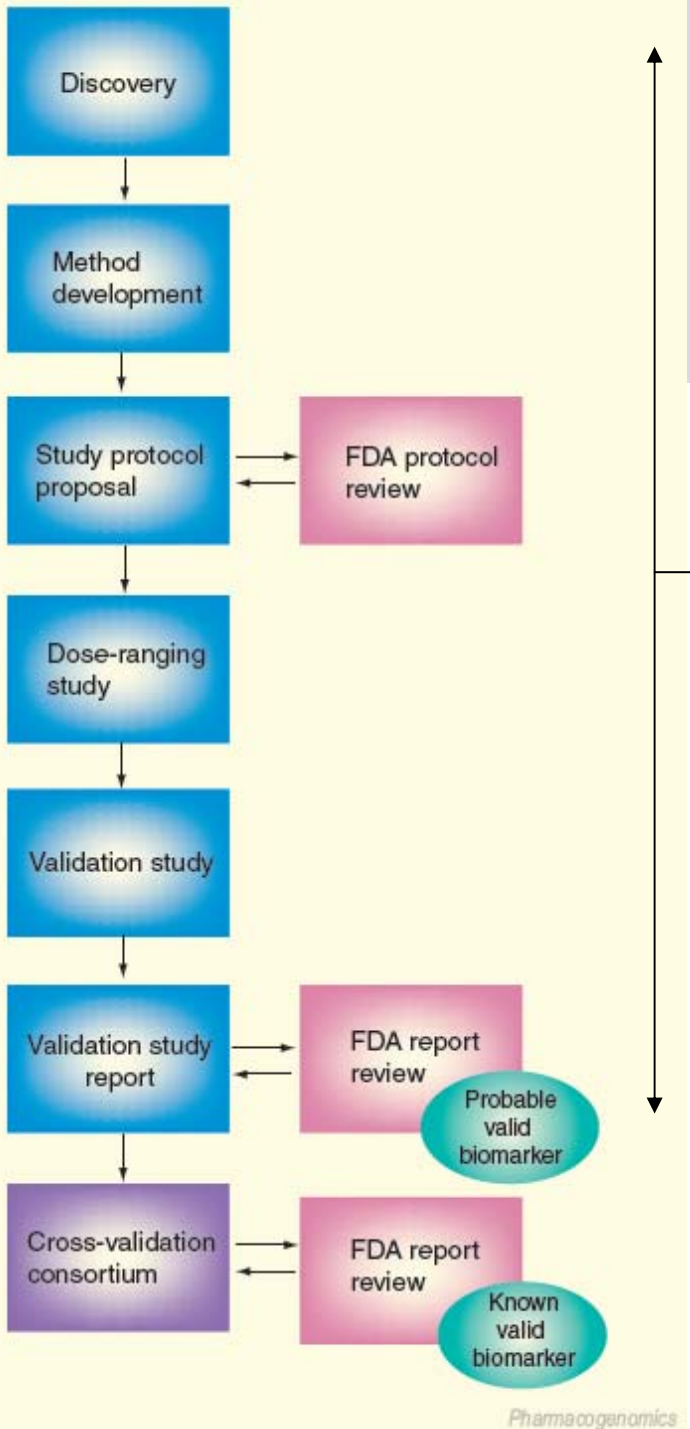
http://www.fda.gov/cder/genomics/

How does an exploratory marker become probable or known valid ?

- Most “known” valid biomarkers have been “validated” by accumulating data over many years
- Markers for “targeted therapies” become known valid when treatment is approved: they are used to demonstrate efficacy during clinical drug development (drug-test co-development)
- FDA Pharmacogenomics guidance does not provide information about marker validation
- Short of clinical trials in drug development process, there are no established processes for marker validation
- Can retrospective data be persuasive for marker validation or are prospective studies required?
- A validation path for pre-clinical markers has been proposed

Biomarker Validation: A Process Map

- Validation of **pre-clinical** genomic biomarkers for drug safety
- CRADA
- Pre-clinical safety testing consortium (PSTC)
- Goal: Regulatory buy-in



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Process map proposal for the validation of genomic biomarkers. Pharmacogenomics. 2006 (5):773-82.

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FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium

Consortium Will Share Tests to Understand Safety of Potential New Drugs Earlier

The Food and Drug Administration (FDA) and The Critical Path Institute (C-Path) today announced the formation of the Predictive Safety Testing Consortium between C-Path and five of America's largest pharmaceutical companies to share internally developed laboratory methods to predict the safety of new treatments before they are tested in humans. The FDA, while not a member of the Partnership, will assist it in an advisory capacity. This unprecedented sharing of potential early indicators of clinical safety may streamline the cost and time of preclinical drug safety evaluation and better inform the use of "personalized medicine". The Consortium was announced today at a press conference detailing the release of the Critical Path Opportunities List – 76 initial research priorities that, if accomplished, will modernize the drug development process by 2010 and help get new medical discoveries to Americans faster and at a lower cost.

- Current membership: 14 large pharmas and Iconix
- Co-directed by C-Path and pharma representatives

Timeline of Predictive Safety Testing Consortium (PSTC)

- Initial discussions started in March 2005 between reps. from OCP Genomics Group and industry, series of informal telecons
- Structural framework proposal by C-Path in July 2005
- Legal framework completed in March 2006
- Four working groups initiated in March 2006 at the SOT Meeting in San Diego
  - Nephrotoxicity, Hepatotoxicity, Vasculitis, Genotoxic and Non-Genotoxic Carcinogenicity
- Launch by Secretary of HHS on March 16, 2006

Assembly of new FDA review teams (umbrella: IPRG) to ensure appropriate regulatory expert review of PSTC data

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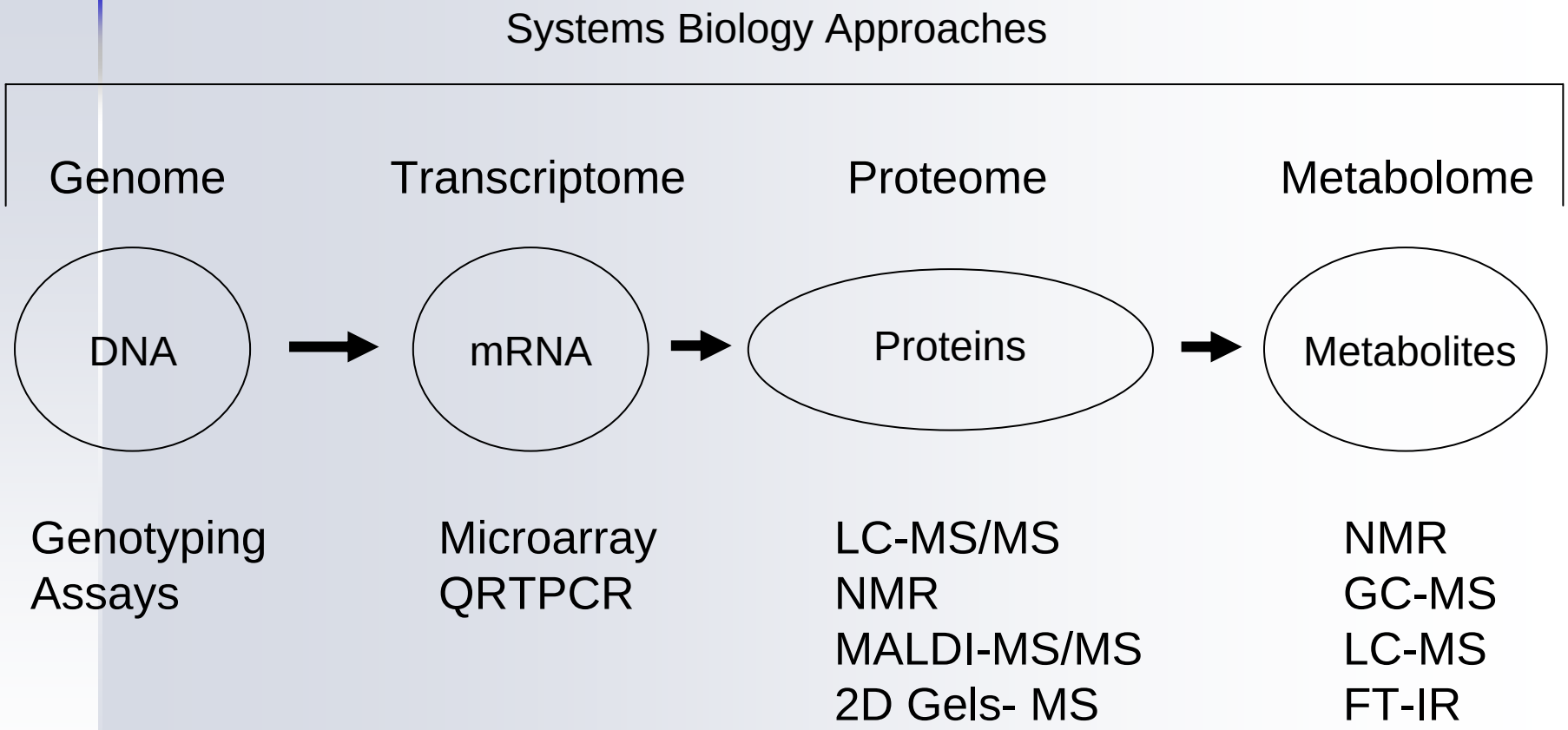
An overview of other “-omic” technologies that could be submitted as a VXDS.



Potential Future Outcomes

Novel Safety Biomarkers for Industry and Regulators

Metabolomic Data and VGDS Submissions……The Future

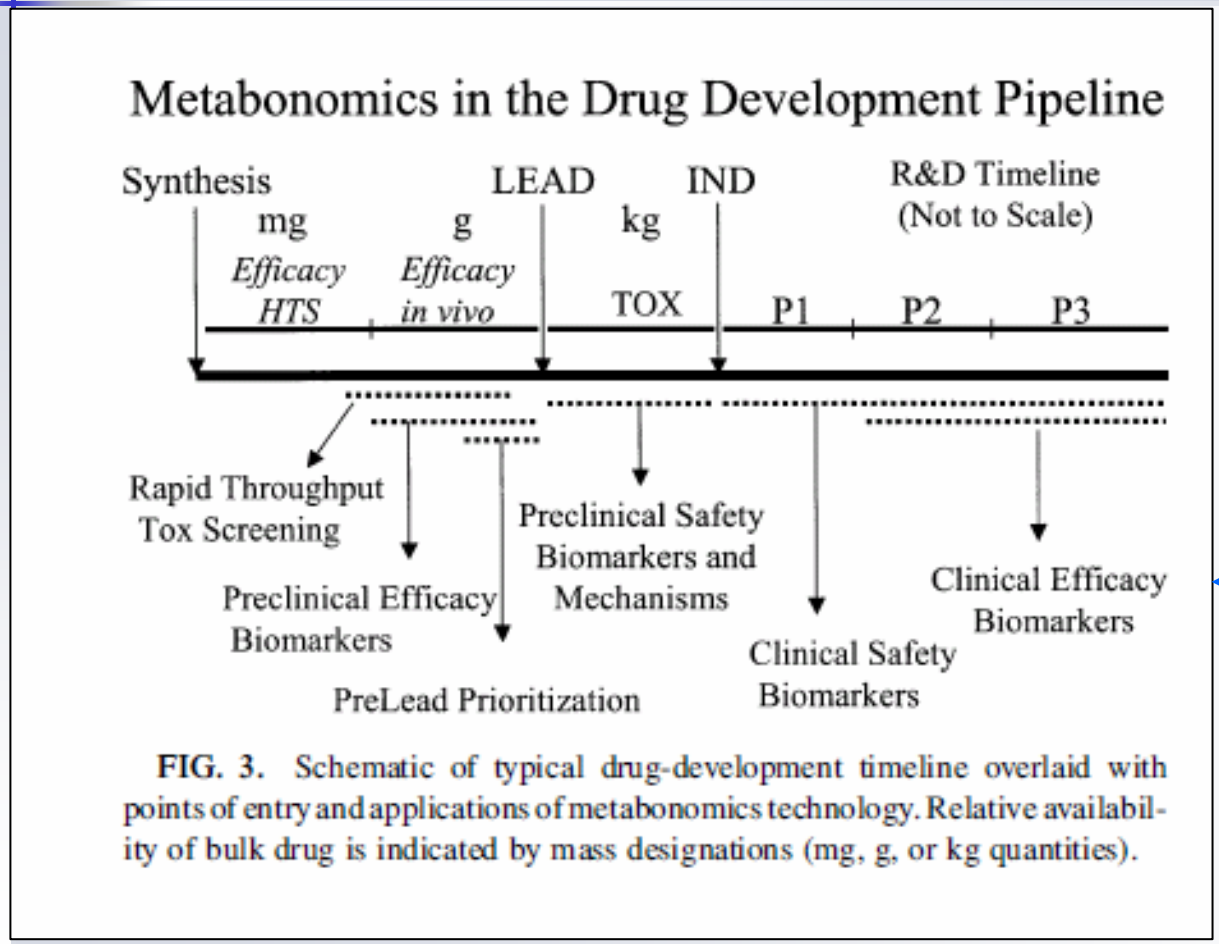


FIG. 3. Schematic of typical drug-development timeline overlaid with points of entry and applications of metabonomics technology. Relative availability of bulk drug is indicated by mass designations (mg, g, or kg quantities).

Technologies

NMR
GC-MS
LC-MS
FT-IR

Robertson, D. G. (2005). Metabonomics in toxicology: a review. *Toxicol. Sci.* **85**(2), 809-822.

Future Directions

- VGDS submissions dealing with multiple types of "-omics" data
  - ✓ Work closely with NCTR on metabolomic and proteomic VGDS projects
  - ✓ NCTR has expertise in generating/analyzing metabolomic and proteomic data
- Continue developing the appropriate IT infrastructure to deal with diverse types of "-omic" data
- FDA has limited experience with metabolomic and proteomic data based on VGDS submissions to date
- ✓ VXDS submission to the FDA will be the first step in the road to biomarker validation
  - ✓ Assess biomarker context proposal

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THANK YOU !

www.fda.gov/cder/genomics

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