Voluntary Genomic Data Submissions: Review and Analysis of Toxicogenomic Data in Preclinical Drug Safety Assessment

Pharmacogenomics Grand Rounds
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Pharmacogenomics Grand Rounds

- Inform about new findings in genomics with relevance to regulatory review and science
- Focus on case examples, should be “hands-on”
- Updates on Voluntary Genomic Data Submissions
- “Late-breaking news”
- No fixed schedule or agenda, planned to be held about 6 times per year
- Organized by OTCOM (Thanks to Karen Zawalick)

Voluntary Genomic Data Submissions:

Review and Analysis of Toxicogenomic Data in Preclinical Drug Safety Assessment

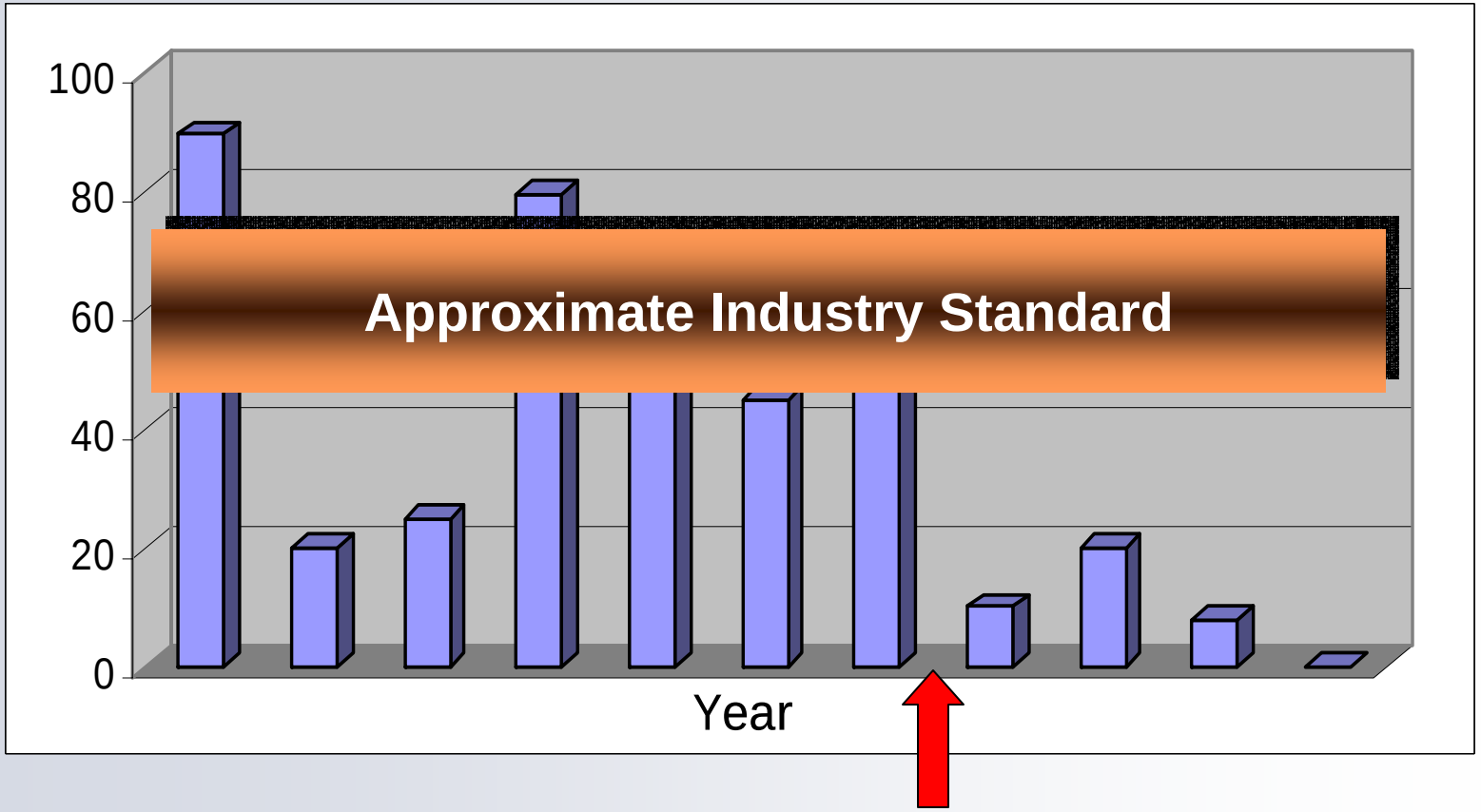
Toxicogenomics

Toxicogenomics is the application of genetic and genomic methods to the study of toxicology

What Is Toxicogenomics ?

- Toxicogenomics is a young science – it became a serious field of research about ten years ago with the broader availability of DNA microarray technology
- Toxicogenomics does not replace “classical” toxicology
- Toxicogenomics can be used in pre-clinical drug development to assess the safety of candidate drugs
- Toxicogenomics has the potential to be a useful tool for regulatory decision making ...
- ... for sponsors *and* for the FDA

Attrition Analysis in Early Drug Development: Effect of Toxicity Testing, Including Toxicogenomic Profiling



Cool. But...

- One could argue that if sponsors use toxicogenomic information to e.g. prioritize compounds for further development, toxicogenomics is their business, not ours.
- That would be short-sighted. Toxicogenomics can be useful for us if we
  - Understand the benefits and shortfalls of the technology
  - Know how to evaluate and interpret the data
  - Have a mechanism that allows sponsors to share this (exploratory) data with us (on a voluntary basis)
  - Are committed to create a regulatory environment that takes advantage of the use of this data

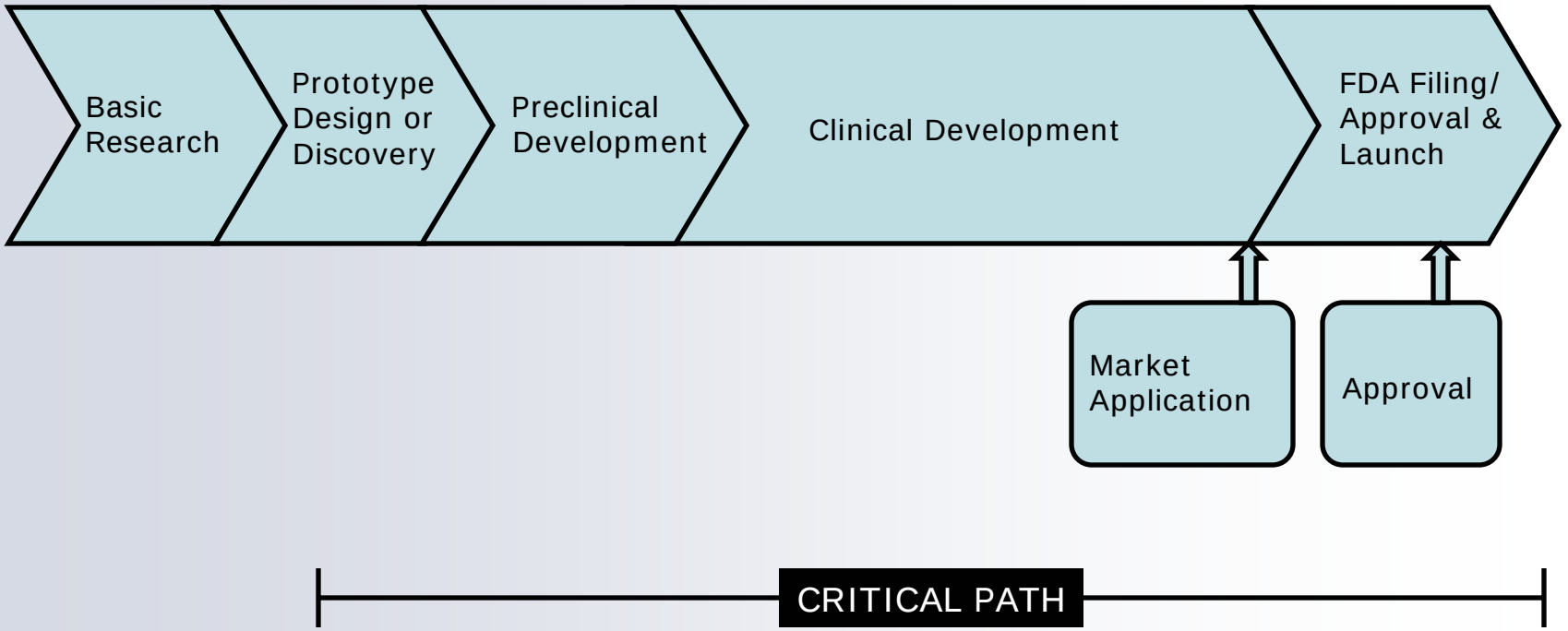
OK. But Why *Should We* Care ?

- If we succeed, we will be able to
  - Better understand the mechanisms of toxicity
  - Predict/detect toxicity earlier
  - Assess pre-clinical toxicity at the molecular level
  - Make better recommendations for pre-clinical safety studies
  - Learn about validating genomic biomarkers
  - Learn about the application and use of new technologies
  - Bring better drugs to patients faster

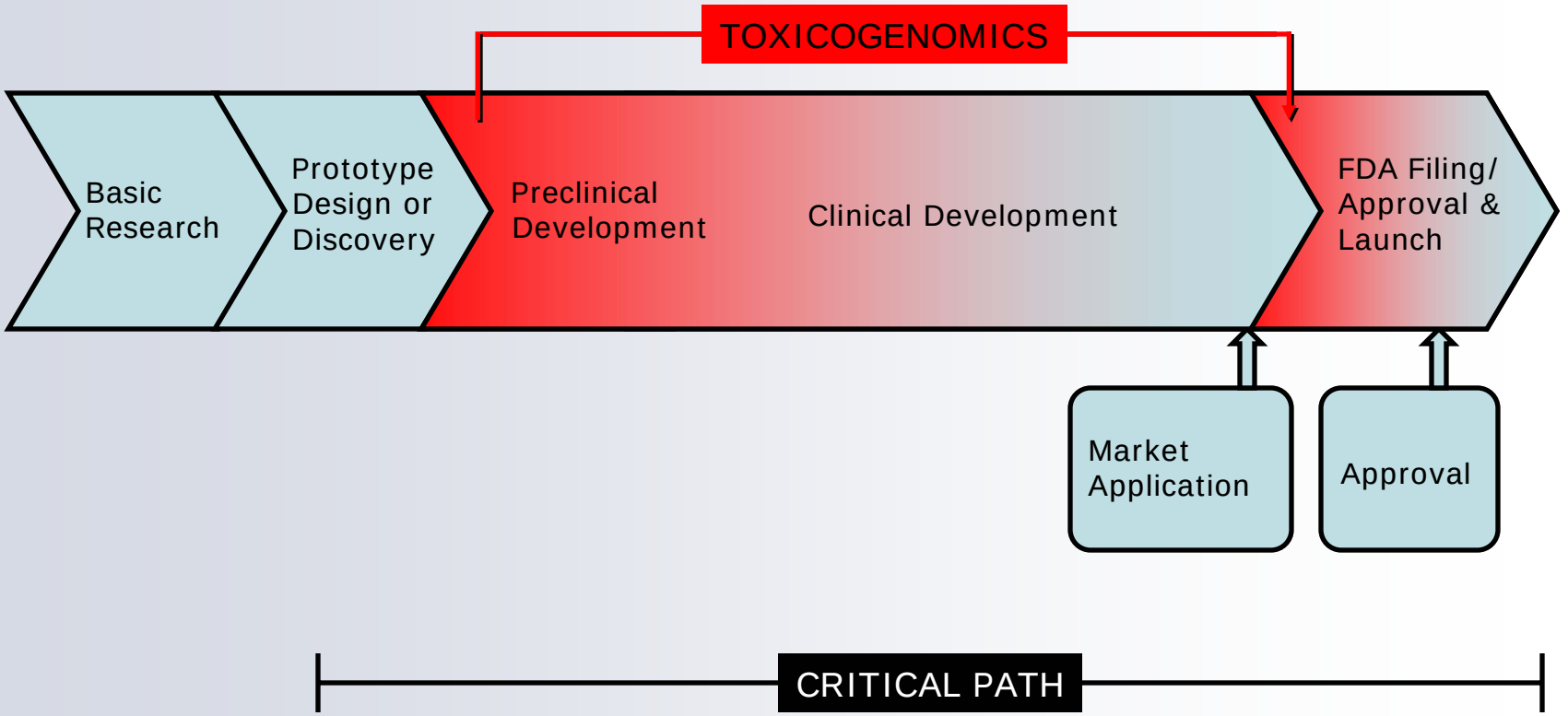
Some of the Issues around *Preclinical* Biomarkers for Safety

- Toxicogenomic markers need to be characterized (validated) rigorously in the context of safety and toxicity:
  - In the context of toxicity, we want to avoid excluding potentially good drug candidates (issue of false positives).
  - In the context of safety, we want to confirm that the absence of a signal corresponds to a safe compound (issue of false negatives).
- Therefore, key questions to address include:
  - Which toxic compounds should be tested
  - Which controls should be used
  - How many toxic and control compounds should be included
  - Which dose (range) should be tested
  - Which time points should be chosen
  - How many replicates are needed
  - Which genes should be included

Stagnation → *Innovation*



Stagnation → Innovation



Guidance for Industry: Pharmacogenomic Data Submissions

www.fda.gov/cder/genomics

www.fda.gov/cder/genomics/regulatory.htm

What Does the PG Guidance Do?

- Introduces a classification for genomic biomarkers
- Clarifies what type of genomic data needs to be submitted to the FDA and when
- Introduces a new data submission pathway to share information with the FDA on a voluntary basis
- Encourages the voluntary submission of exploratory genomic data
- Introduces new agency-wide PG review group (IPRG)
- Clarifies how the FDA will review genomic data submissions

What Does the PG Guidance *Not* Do?

- Does not provide information on how to validate genomic biomarkers
- Does not provide information on how to use genomic biomarker during drug or device development process (scientific vs. regulatory guidance)
- Does not expand into other "-omics' areas such as proteomics or metabolomics
- Does not equal genomic data with voluntary data
- Does not create new processes for the review of required data submissions

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

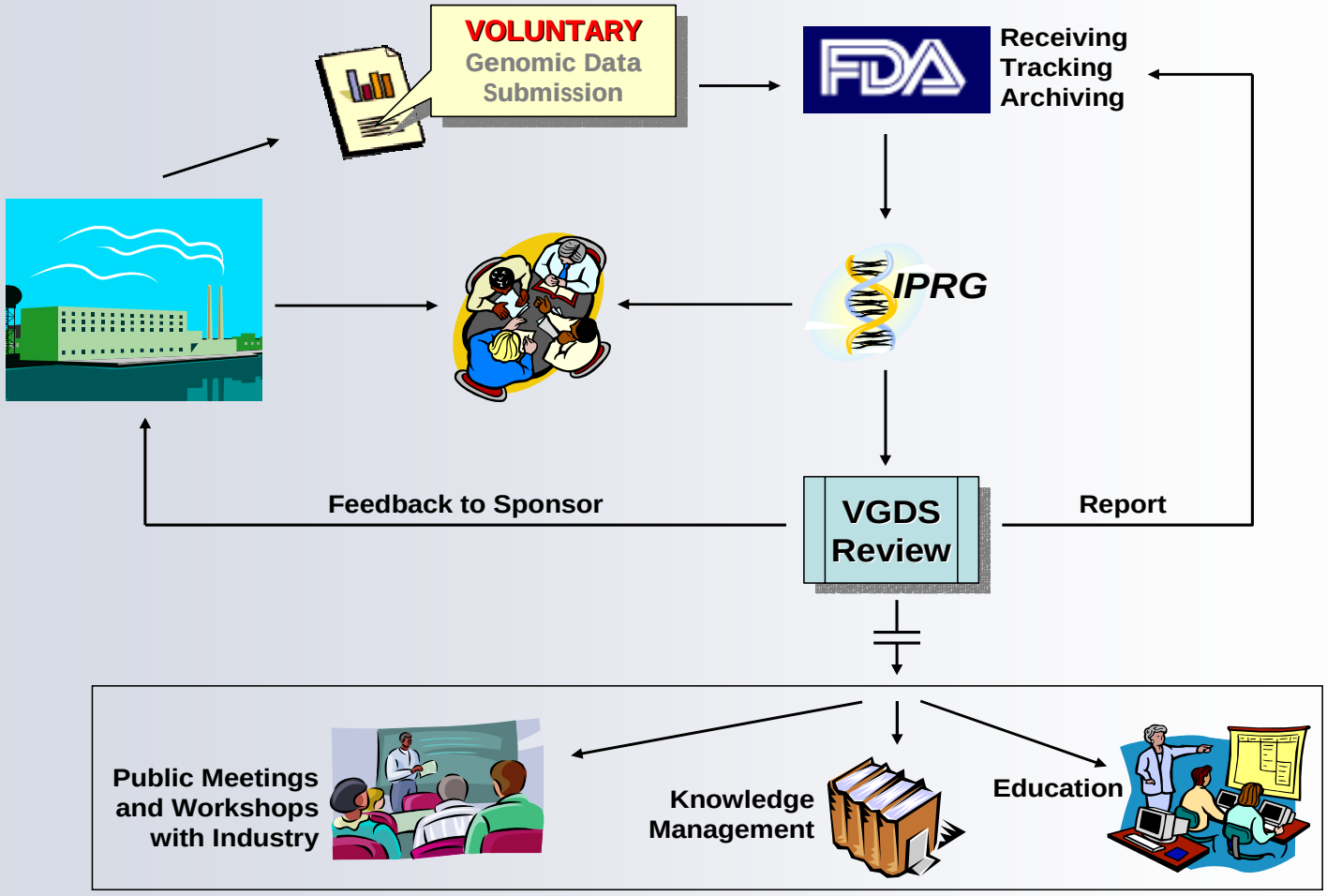
Classification of Biomarkers, cont'd

- **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

VGDS: A Unique Data Submission Path

- Submission of **exploratory** PG data submission regardless if subject of an active IND, NDA, or BLA
- Data may result from, e.g., DNA microarrays, single or limited gene expression profiles, genotyping or SNP profiling, or from other studies using evolving methodologies
- Intent to build expertise and foundation for developing scientifically sound regulatory policies
- VGDS creates a forum for scientific discussions with the FDA outside of regular review process
- Data not used for regulatory decisions

VGDS Review Process



Update: VGDS Program So Far

- VGDS statistics:
  - 25 submissions received
  - 15 sponsor meetings held (2 bilateral with EMEA)
  - 5+ submissions informed to be submitted
- Impact:
  - Overall feedback: 4.5 out of 5 (formal survey)
  - Multiple submissions from single sponsor
  - Follow-on submissions
  - Great interest in bilateral meetings

Examples of VGDSs

- Candidate gene approach vs. whole genome SNP scan
  - Statistical approach feasible?
  - Which SNPs to take forward?
  - Mechanistic explanation
- Gene expression profile in peripheral blood
  - Can expression profile be obtained?
  - Is it predictable?
- Gene expression pattern as genomic biomarker to predict responders and non-responders
  - Hypothesis vs. validation
  - Statistics
  - Clinical utility

VGDS Experience

- Sponsors use voluntary submissions to “test the water”
- Excellent opportunity for both parties to educate
- Hands-on policy development (consistency and communication across therapeutic areas: genomics as a matrix function)
- Number and quality of submissions demonstrates that industry is serious about use of genomics in drug development
- Some uncertainty about regulatory impact remains

VGDS Typical Questions

- Statistical approach feasible?
- Which SNPs to take forward?
- Mechanistic explanation?
- Can expression profile be obtained?
- Is the profile predictable for outcome?
- How can we test the hypothesis and how can it be validated?
- Will this approach provide us with a clinically useful answer?

Voluntary Genomic Data Submissions: Review and Analysis of Toxicogenomic Data in Preclinical Drug Safety Assessment

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Office of Clinical Pharmacology and Biopharmaceutics
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Toxicogenomic Applications Today: Biomarker Types

- ***DMPK*** **– transcriptional regulation of P450s, drug transporters, secondary effects on metabolism, endocrine, etc.**

- ***Pharmacology*** **– known, expected, or biologically compelling efficacy markers.**

- ***Correlation with NOEL*** **– global expression profile as a marker of significant histopathologic or other toxic effect.**

- ***Mechanism of toxicity*** **– transcription in target vs. non-target tissues, elucidation of time and dose response, characterization of transcription relative to tool positive/negative control compounds, pathways, pathology score, etc.**

Non-Clinical Toxicogenomics Impact: *genomic biomarkers contribute to a weight of evidence or provide a starting point for hypothesis testing*

Genomic Biomarker Category	Impacted Programs
% Altered transcripts; treated vs. control vs. NOAEL	**30%**
Transcription of P450s, drug transporters vs. DMPK	**25%**
Biomarkers of pharmacology vs efficacy or tox	**45%**
Diagnostic markers of histopathology endpoints	**30%**
Predictive markers of histopathology endpoints	**15%**
Predictive markers of toxicity (Iconix, Genelogic)	**10-15%**

Toxicogenomics in Voluntary Genomic Data Submissions (VGDS)

- **Toxicogenomics in VGDS**
  - **Goals of a VGDS**
    - **Exchange pharmacogenomic or toxicogenomic information.**
      - ***What is the best way to get it?***
      - ***What does it mean?***
    - **Exchange application information.**
      - ***Where can we apply pharmacogenomic and toxicogenomic information to improve drug development?***
      - ***What hurdles need to be overcome to standardize measurements and interpretations associated with pharmacogenomic and toxicogenomic information?***

Toxicogenomics in Voluntary Genomic Data Submissions (VGDS)

- **Toxicogenomics in VGDS**
  - **Goals of Toxicogenomics**
    - **Improved understanding of safety profile for candidate compounds.**
      - ***Understanding of mechanisms in animal models.***
      - ***Understanding of potential safety issues in humans.***
    - **Development of predictive biomarkers**
      - ***Accessible biomarkers for preclinical and clinical applications.***
      - ***Model-specific biomarkers for improved sensitivity and accuracy in preclinical drug safety assessment.***

Toxicogenomics in Voluntary Genomic Data Submissions (VGDS)

- Reviewer training in the statistical analysis of hybridization data
  - Analysis tool (Rosetta Resolver, ArrayTrack, DrugMatrix)
  - Analysis protocol
    - Normalization
    - P-value
    - Fold-change
  - List of statistically significant genes
- Biological interpretation of statistically significant gene list (DrugMatrix, Ingenuity)
- Toxicogenomic interpretation of statistically significant gene list.

Summary of Toxicogenomic Data in VGDS

- Three toxicogenomic VGDS data submissions received thus far. Analyses completed for two of these.
- Three to six compounds
- One rat study per compound
- Data received include both Affymetrix chips as well as quantitative PCR gene expression platforms.
- Exploratory genomic biomarkers.
- Application for compound prioritization in research.

Data Sample

Toxicology: Compound 1

finding	grade	control	Compound 1
Stomach/inflammation/subacute/focal/pyloric	1	1/6 (1M)	3/6 (3M)
Thymus/hemorrage/focal	1	1/6 (1M)	2/6 (2M)
Thymus/hemorrage/multifocal	1	1/6 (1M) 0/6 (0F)	2/6 (2M) 3/6 (3F)
Thymus/hemorrage/multifocal	2	0/6 (0F)	1/6 (1M)
Mandibular lymph nodes/hemorrage/focal	1	0/6 (0F)	1/6 (1F)
Mandibular lymph nodes/hemorrage/multifocal	1	1/6 (1F)	2/6 (2F)

Toxicology: Compound 1

- **Comments from Pharm/Tox reviewers:**

1) Submission is generally satisfactory for the purpose of this exercise but might not be for a formal submission.

2) No rationale for dose selection.

3) Histopathological findings may prove to be more significant at higher doses or as a result of longer treatment.

4) Only males were used for toxicogenomic studies. Females might respond differently.

Conclusions for Compound 1 Hepatic Toxicogenomic Data

- **Most functions and pathways identified are mapped with less than 3 genes.**
  - **An accurate biological interpretation for the statistically significant gene list is not likely for these data.**
- **Canonical signaling pathways identified may be related to pharmacology of Compound 1.**
- **Sponsor did not submit toxicogenomic data for target tissues.**

Toxicology: Compound 2

finding	grade	control	Compound 2, *low dose*	Compound 2, *medium dose*	Compound 2, *high dose*
Psoas major					
Degeneration/ necrosis	**1**	**2/12 (1M/1F)**	**6/12 (4M/2F)**	**7/12 (4M/3F)**	**6/12 (2M/4F)**
Degeneration/ necrosis	**2**	**0/12**	**0/12**	**0/12**	**2/12 (2M)**
Biceps femoris					
Degeneration/ necrosis	**1**	**1/12 (1M)**	**1/10 (1M)**	**0/12**	**2/12 (2M)**

Toxicology: Compound 2

- **Comments from Pharm/Tox Reviewers:**

  1) The draft report would not be adequate for a formal submission (no table of contents, no pagination, no summary tables).

  2) There were discrepancies in data presented within the text and histopathology tables.

  3) Don't agree with the NOAEL.

  4) No information about metabolism especially in view of a decrease in exposure on day 14 and possible effects on CYP450.

Conclusions for Compound 2 Toxicogenomic Data

- **Skeletal and muscular disorder gene expression changes identified in both the psoas muscle as well as in the liver data.**
  - **Arthritis: > 5 genes, dose effect.**
  - **Hypertrophy: dose effect.**
- **Subset of genes identified that correlates with myopathy.**
  - **This subset includes signaling pathways absent in the subset for drug presence without myopathy.**

Toxicology: Compound 3

- **Comments from Pharm/Tox Reviewers:**

1) Draft report contained only summaries (inadequate for a formal submission).

2) No rationale for dose selection; however, toxicities were observed with selected doses (mostly at mid- and high doses).

3) Concur with reported toxicology findings.

Conclusions for Compound 3 Toxicogenomic Data

- **Dermatological disease-associated gene expression changes identified in the liver and skin data.**
- **Hepatic disease-associated gene expression changes identified in liver data.**
  - ***Inflammation*: > 10 genes, dose effect.**
  - ***Hepatic System Disorder*: > 10 genes, dose effect.**
  - ***Steatosis*: > 10 genes, dose effect.**

Q&A Summary

Q&A: *reproducibility of analysis.*

- **Are we able to reproduce the induction or repression ratio data provided in the submission?**
  - **Yes. Our match of the sponsor analysis matched the list of statistically significant genes. Alternative analyses also matched biological conclusions from the original analysis.**
- **Are ratios for induction or repression (fold-change and p-values) and those obtained by other methods used to normalize array data and calculate fold-change and p-values considered to be comparable?**
  - **Yes.**

Q&A: *dose-response*

- **Do we see dose-responsive behavior for transcriptional regulation of gene subsets in the study?**
  - **Yes. We were also able to match these subsets to the biological pathways proposed by the sponsor.**
- **Can we agree that gene toxicogenomicophobic transcripts appear statistically significantly modulated, and that these changes, though significant, are of unknown significance given the absence of corroborative traditional endpoints?**
  - **We agree both that significant expression changes associated with gene toxicogenomicophobic transcripts were detected, as well as with the conclusion that the toxicological reports for this study do not show corroborative evidence with traditional endpoints. A study protocol with a longer exposure to the compound tested would help confirm this conclusion for this compound.**

Q&A: *expression profiles*

- **Are we able to reproduce a comparative analysis relating most similar expression profiles to transcripts known to be modulated by gene toxicogenomicophobic?**
  - **Not in DrugMatrix, but yes in Ingenuity.**

- **Can we identify a comparable set of transcripts to those reported to be consistently regulated across multiple tissues? Can we agree with the interpretation that these markers are likely to be related to the pharmacologic action of the drug?**
  - **We identified a set of several transcripts across all tissues in this study.**
  - **A pharmacologic role for these might be expected form their identification across different tissues.**

Q&A: *precedents*

- **Can we identify a similar set of potential toxicity-associated transcripts as reported by others?**
  - **A set was identified, but it included neither troponin nor ankyrin.**
- **Do we agree with the interpretation that study data and study analyses do not identify specific, predictive biomarkers of drug-related toxicity?**
  - **We agree that a more comprehensive study protocol than the one presented would be needed to confirm the proposed signature across multiple drugs and their corresponding controls.**

Q&A: *policy*

- **Is there a QC threshold for acceptance of hybridization data?**
  - **A consensus threshold is needed for this metric to assess hybridization quality. The MAQC Consortium is working on the identification of consensus threshold.**
- **Do we see transcriptomic data uniformly adding value to traditional analyses?**
  - **Yes. As part of the weigh of evidence presented, the transcriptomic data extends our biological understanding of traditional endpoints. Additional studies in the future would extend the value of the transcriptomic data as genomic biomarkers.**
- **Do we see cause for safety concerns in any studies not clearly identified by traditional toxicologic investigations?**
  - **No, although further experimental evidence for potential markers as well as for the expression changes reported in this study would better define the value of these as exploratory biomarkers.**

What is there beyond toxicogenomic VGDS?

- **From exploratory to known:** ***how should we validate toxicogenomic biomarkers?***

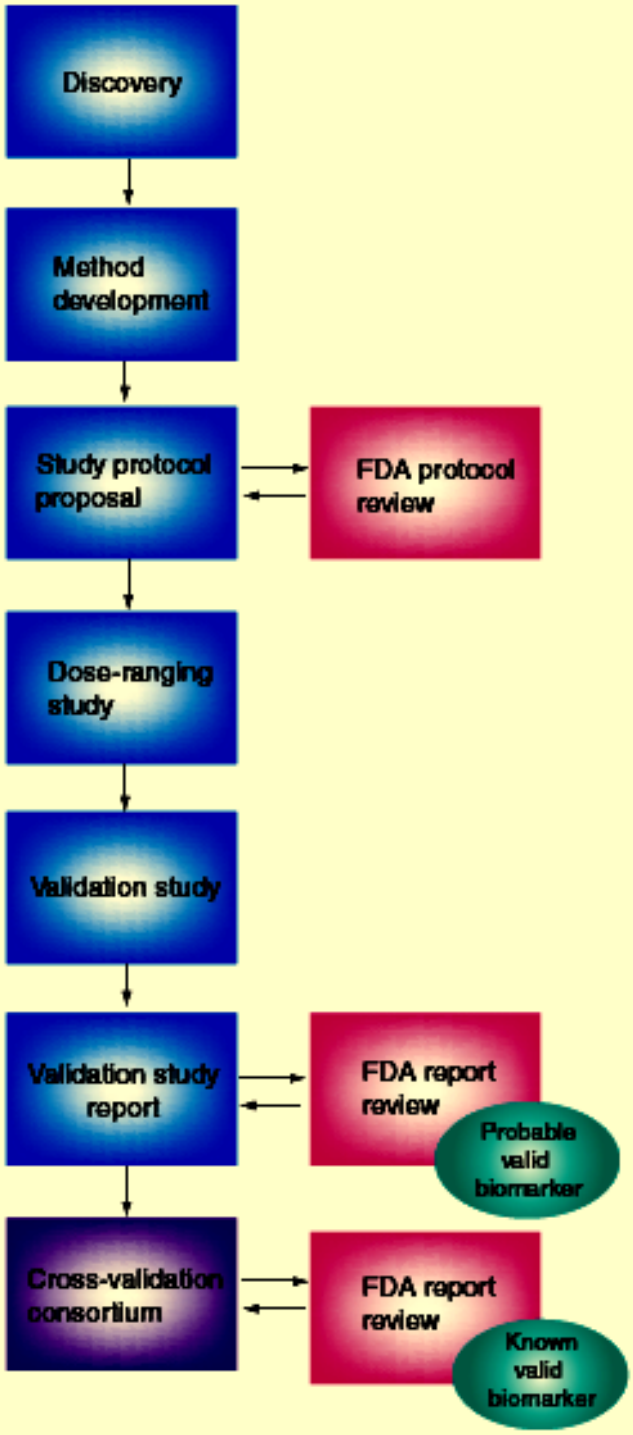
Submitting data to an:	IND	New (Unapproved) NDA, BLA, or Supplement	Previously Approved NDA or BLA
Known Valid Biomarker	Must be submitted, pursuant to 21 CFR 312.23 (a) (8), (9), (10) (iv) or (11).	Must be submitted, pursuant to 21 CFR 314.50 and 601.2. See section IV.B. of the guidance.	Must be submitted pursuant to 21 CFR 314.81 in annual report and should be submitted pursuant to § 601.12 as synopses or abbreviated reports.
Probable Valid Biomarker	Does not need to be submitted.[9] The FDA welcomes voluntary submission of such data in a VGDS.	The FDA recommends submission, using algorithm in section IV.B. of the guidance.	Must be submitted pursuant to 21 CFR 314.81 in annual report and should be submitted pursuant to § 601.12 as synopses or abbreviated reports.
Exploratory or Research Pharmaco-genomic Data	The FDA welcomes voluntary submission of such data in a VGDS.	The FDA recommends submission, using algorithm in section IV.B. of the guidance. The FDA welcomes voluntary submission of such data in a VGDS.	The FDA welcomes voluntary submission of such data in a VGDS.

Genomic Biomarkers: *Validation Ease*

Genomic Biomarker Category	Validation Ease
% Altered transcripts; treated vs. control vs. NOAEL	**1**
Transcription of P450s, drug transporters vs. DMPK	**1**
Biomarkers of pharmacology vs efficacy biomarkers	**2**
Diagnostic markers of histopathology endpoints	**3**
Predictive markers of histopathology endpoints	**4**
Predictive markers of toxicity (Iconix, Genelogic)	**5**

5 = most difficult

Genomic Biomarkers: *Validation Process Map Proposal*



Key Future Activities in Toxicogenomics

- Bridging activities even when not validated, e.g. VGDS, C-Path, pipeline decision making with unvalidated transcriptional markers.
- Increased toxicogenomics-related publications/presentations, encouraging toxicogenomics study disclosure.
- Financial support for development of toxicogenomics review tools.
- Better definition of the discipline, working towards standards, recommending curricula.

Pipeline decision-making with unvalidated transcriptional markers.

- ***Sponsor Activities***
  - **Candidate ranking in drug research.**
  - **Mechanistic understanding of toxicity findings.**
  - **Species-specific pathway analyses.**
  - **Human pathway risk analyses.**
- ***Reviewer Activities***
  - **Relative risk assessment for multiple drugs in the same class.**
  - **Mechanistic understanding of toxicity findings.**
  - **Species-specific pathway analyses.**
  - **Human pathway risk analyses.**

Encouraging toxicogenomics study disclosure.

- ***Sponsor Activities***
  - **Research consortia in toxicogenomics.**
  - **Validation consortia in toxicogenomics.**
  - **Publication of study results.**
  - **Submission of validation data for acceptance by the FDA.**
- ***Reviewer Activities***
  - **VGDS data review and interpretation.**
  - **Input into study protocol and execution.**
  - **Publication of study results.**
  - **Comprehensive and expedited review of validation package.**

Financial support for development of toxicogenomics review tools.

- ***Sponsor Activities***
  - **Support development of tool for biological interpretation of gene expression data in toxicogenomics.**
- ***Reviewer Activities***
  - **Work with reference database platform developers such as Ingenuity on tools for biological interpretation of gene expression data in toxicogenomics.**
  - **Work with empirical database developers such as Iconix and GeneLogic on tools for biological interpretation of gene expression data in toxicogenomics.**

Better definition of the discipline, working towards standards, recommending curricula.

- ***Sponsor Activities***
  - ***Better Definition of the Discipline:*** **application of consensus practices in toxicogenomics.**
  - ***Working Towards Standards:*** **application of consensus standards in toxicogenomics.**
  - ***Recommending Curricula:*** **integrated corporate training across therapeutic and fiunctional areas on toxicogenomics.**
- ***Reviewer Activities***
  - ***Better Definition of the Discipline:*** **development of consensus practices intoxicogenomics.**
  - ***Working Towards Standards:*** **participation in consortia such as MAQC and ERCC for development of consensus standards in toxicogenomics.**
  - ***Recommending Curricula:*** **integrated reviewer training across therapeutic areas on toxicogenomics.**
    - **Tools and Concepts**
    - **Case Studies**
    - **ArrayTrack**

Summary

- **Toxicogenomic data can be useful for regulatory review, i.e. the assessment of drug safety, if we understand the benefits and shortfalls of the technology.**

- **Toxicogenomic VGDS help us to understand this technology, as well as the science and review criteria for toxicogenomic data. It also helps us to understand a sponsor's strategy to assess which compounds to move forward in the drug development process and why.**

- **The validation of toxicogenomic biomarkers, and the formulation of a validation path, are important for consensus-building in the application of toxicogenomics in drug development and regulatory review.**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